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EPIDEMIC KERATOCONJUNCTIVITIS ("SHIPYARD CONJUNCTIVITIS")

I. ISOLATION OF A VIRUS

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In 1941 in the San Francisco shipyards there occurred on outbreak of an acute inflammatory disease of the eyes, apparently derived from a similar outbreak in Hawaii,[1] which soon spread throughout the Pacific coast area and which eventually reached the east coast. A complete clinical study of the disease has been reported by Hogan and Crawford,[2] who called it "epidemic keratoconjunctivitis." A similar type of acute keratoconjunctivitis has been variously described since 1890 under different names in Austria, Germany, India and the Orient. The question remains as yet unanswered whether all the reports have reference to the same disease.

Two things can definitely be said about the disease: 1. Its causation is unknown, although evidence points to a nonbacterial agent. 2. It is obviously infectious in nature, although according to Hogan and Crawford it is transmissible only by direct contact to susceptible persons. On the other hand, there seems every reason to believe that epidemic keratoconjunctivitis is capable of inflicting moderately severe ocular damage on large portions of the population in the affected areas, since reports mention from 3,000 to 10,000 cases.[3]

As seen in New York the disease appears typically as an acute follicular conjunctivitis with swollen and sometimes painful preauricular nodes. In cases of severe involvement the conjunctiva is extremely

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This investigation was undertaken in informal collaboration with the Commission on Neurotropic Virus Diseases, Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army.

1. Holmes, W. J.: Hawaii M. J. **1**:11, 1941.
2. Hogan, M. J., and Crawford, J. W.: Am. J. Ophth., to be published.
3. Personal communication to Dr. P. Thygeson.

congested and chemotic and transient pseudomembranes may appear. The lids, in particular the upper lid, are also edematous. Although it is difficult to compute the incubation period, symptoms may appear four to five days after exposure. The differential diagnosis lies between inclusion conjunctivitis and Béal's acute follicular conjunctivitis. In the first disease, typical inclusion bodies can be demonstrated in the conjunctival scrapings, the enlargement of the regional lymph node is not marked and recovery follows quickly on administration of sulfonamide compounds. Although the disease closely resembles Béal's conjunctivitis it is differentiated by its greater severity, its corneal complications and its prolonged course. When keratitis did occur, it resembled that reported by Hogan and Crawford and, of course, introduced the symptoms of lacrimation, photophobia and pain.

As in inclusion conjunctivitis and Béal's conjunctivitis, the results of bacteriologic studies of the conjunctival scrapings in the cases discussed in this paper have been essentially negative, showing either no organisms at all or occasional saprophytes, such as Staphylococcus albus or diphtheroids. The cells of the exudate have been typically mononuclear.

Eleven cases were studied experimentally. Of these the diagnosis seemed fairly certain in 9. When conjunctival scrapings from the patients were injected into white Swiss mice intraperitoneally and intracerebrally, certain vague symptoms were noted in 6 cases in forty-eight to seventy-two hours. Rough coat and lethargy were prominent features of the syndrome, and there was a tendency toward a humped back, but the mice recovered in most instances, and transmission of symptoms was successful only for two, three, four or five mouse passages.

Because of the inability to maintain an infection in mice, the following procedure was carried out when a patient with a fresh inflammation was seen in the clinic: After injection of conjunctival scrapings produced the symptoms noted previously, brain emulsion from the second mouse passage was put into tissue culture (embryonic mouse brain tissue in serum ultrafiltrate [4]) and incubated at 37 C. for three days. This culture brought down mice in two to three days, and not only were the symptoms more definite but the animals appeared to go through a distinct course of disease; i. e., the degree of illness became correspondingly severe once it had been initiated, and death occurred in twenty-four to thirty-six hours. Subculture again proved infectious. At this stage the tissue cultures were divided into two groups, one being incubated at 37 C. for three days and the other at room temperature for eight days. The 37 C. series was not infectious after the fourth culture passage, but the agent appeared to grow at room

4. Sanders, M.: J. Exper. Med. **71**:113, 1940. Sanders, M., and Jungeblut, C.: ibid. **75**:631, 1942.

temperature, since cultures maintained at that temperature continued to be infectious. A possible explanation for this fact, based on 3 experiments, may be that the infectious agent is intracellular and can be lost easily if only the supernatant fluid is subcultured. In view of experience to date, it seems probable that the potency of the 37 C. cultures was not high and the supernatant fluid was consequently free from the agent. At room temperature, on the other hand, with a higher potency, it is possible that infection spread from the cells to the extracellular menstruum. The room temperature series is now in its thirteenth tissue culture generation and is infectious for mice by the intracerebral route. But even at room temperature, serial cultivation is best obtained by using as subculture inoculum a mixture of ground up cells and fluid. Passage from mouse to mouse after infection with tissue culture has yielded a fairly potent strain with a titer at 10^{-5} or 10^{-6}, bringing down mice with uniform regularity. The incubation period has continued to be two to three days for low dilutions and extends to six or seven days for higher dilutions.

The symptoms in mice are as follows: At first the animal is lethargic and has a ruffled coat. Within three days post inoculation, tonic and clonic convulsions may be observed. Occasionally spastic paralysis occurs. Once the virus is "fixed" in mice, illness terminates in death. Adult mice may be infected only by intracerebral and intranasal inoculations. In the case of unweaned mice, however, the age factor of susceptibility, similar to that seen in St. Louis encephalitis and in equine encephalomyelitis, is present, and infection by the intraperitoneal route is possible.

The pathologic picture in mice is not striking and may be described generally as follows:

Scattered irregularly through the gray and white matter of the cerebrum and the brain stem, and less frequently in the cerebellum and the spinal cord, are small focal inflammatory lesions. These consist essentially of perivascular infiltration by lymphocytes or occasionally by polymorphonuclear leukocytes. There is also a diffuse moderate infiltration of similar type in the perivascular parenchyma. In some instances polymorphonuclear leukocytes predominate in the lesions. In these instances neural elements in the immediate vicinity of the perivascular infiltration show acute degenerative changes, and there is early proliferation of microglia cells. No lesions are found in any other organs.

Thus, while the pathologic picture in mice is not unique, it is, nevertheless, quite different from the pictures in the infections caused by the more common latent mouse viruses which are found as contaminants in the laboratory, e. g., lymphocytic choriomeningitis, spontaneous mouse encephalomyelitis of Theiler and meningopneumonitis. The pathologic picture also need not be confused with that of other virus infections transmitted to mice, such as herpes, equine encephalomyelitis, lymphogranuloma venereum and rabies.

The host range is not limited to Swiss mice. Guinea pigs and rats have shown no signs of infection after intracerebral, intraperitoneal or intraconjunctival injection of virus, even though all types of inoculation have been combined in individual animals. Preliminary studies have indicated that rabbits are susceptible.

Intraconjunctival injection into 2 Macacus rhesus monkeys produced a transient but definite catarrhal conjunctivitis. No enlarged preauricular node was present in the animals. The inoculum consisted of a mixture of brain emulsion from the third mouse passage and tissue culture. On one occasion the conjunctivitis was effected by merely dropping the tissue culture and mouse brain mixture into one eye. However, repetitions of the monkey experiments with virus from later passages gave negative results.

A human volunteer, a normal healthy man, received two doses of virus-containing material. The first application of virus (about 3,000,000 mouse doses) produced no symptoms for three days, but on the fourth day a mild conjunctivitis occurred which did not have the clinical characteristics of epidemic keratoconjunctivitis. At this time (fourth day after the first inoculation), a second application of virus material was made on the same eye. There was no change in the appearance of the eye until the end of the third day, when the conjunctivitis became somewhat more severe. By the fourth day, a typical picture of epidemic keratoconjunctivitis appeared. The lids became edematous, there were some lacrimation and tenderness over the affected eye, the conjunctiva of the lower lid was hypertrophied and edematous and a definite enlargement of the preauricular node was observed.

That the agent under investigation belongs to the group of viruses is indicated by the following evidence:

1. Routine aerobic and anaerobic cultures from the mouse brain and from the tissue cultures have yielded no organisms.

2. Infectivity is not maintained if living cells are not present in the culture medium. Furthermore, pleuropneumonia is ruled out because the agent will not grow in 10 per cent horse serum broth, and dark field examination of this preparation gives entirely negative results.

3. Infectivity is not lost after the culture is passed through collodion membrane filters of the order of magnitude of 75 to 100 millimicrons, showing that, according to Elford's calculations, the infectious particles must be appreciably smaller than 50 millimicrons. No filtration end point has as yet been reached.

NEUTRALIZATION TESTS

Since epidemic keratoconjunctivitis is a disease characterized by at least one to three months' duration, and since the lymph node enlargements suggest a good antigenic stimulus, it is to be expected that

patients suffering with this disease will have circulating antibodies. Several neutralization experiments have been carried out with serum of patient E. L., from whose conjunctiva the virus discussed here was presumably isolated. It was at once apparent that neutralizing antibodies could not be demonstrated if the intracerebral technic was used. The best results were obtained with serum-virus mixtures kept for one hour at 37 C. and for four hours in the refrigerator and then injected intraperitoneally into unweaned mice.

With this technic neutralizing antibodies were demonstrated in the serum of patient E. L. The antibody titer varied from 100 to 1,000 neutralizing doses. In four tests the serum-virus control (normal human serum) titrated to 10^{-5} or 10^{-6}, while under the same conditions a mixture of virus and serum from patient E. L. gave titers of 10^{-2} and 10^{-3}. It should also be noted that on one occasion serum from another patient who had recovered from a severe attack of epidemic keratoconjunctivitis showed between 100 and 10,000 neutralizing doses. However, in the same experiment, serum of a third patient, apparently also recovered from the disease, contained no neutralizing antibodies. The neutralizing results were quite distinct and were based not only on symptoms but on the deaths of the animals.

Additional control serums consisted of a potent antilymphocytic choriomeningitis serum, one which was known to contain Theiler neutralizing antibodies and an antiherpetic serum. None of these serums had any neutralizing effect on the virus.

CONCLUSIONS

A possible specific agent for epidemic keratoconjunctivitis has been isolated. The agent in question appears to belong to the virus group. The evidence in favor of its specific nature is as follows:

1. Material taken directly from the conjunctiva of a patient suffering with this disease produced, when injected intracerebrally into Swiss mice, symptoms similar to those previously obtained under the same clinical and experimental conditions.

2. The infectious agent was maintained when brain emulsion from the second mouse passage was put into tissue culture. Serial subcultivation was possible only at room temperature and by use of ground up tissue culture as inoculum.

3. A human volunteer receiving the mouse virus in his conjunctiva responded in four days with a mild conjunctivitis. This incubation period is similar to that recorded for the disease in human beings. When mouse virus was again applied to the same eye, there was observed four days later a typical picture of epidemic keratoconjunctivitis.

4. The pathologic picture in mice is not unique but, nevertheless, does not resemble that in other common virus infections.

5. Definite neutralization of the agent was obtained when it was mixed with serum of a patient who supplied the original material. The neutralizing power of the serum varied from 100 to 10,000 mouse doses. The serum of another patient, also recovered from epidemic keratoconjunctivitis, contained definite neutralizing antibodies.

Against the specific nature of the isolated agent may be considered the following evidence:

1. In spite of the fact that the original material passed through only 2 mice, the presence of a contaminating latent mouse virus should be more surely excluded by exhaustive tests. Attempts are being made to satisfy this objection.

2. A third patient who had apparently recovered from epidemic keratoconjunctivitis failed to show neutralizing antibodies. It is obviously desirable and essential to perform additional neutralizing tests with this virus and serum from patients known to have had epidemic keratoconjunctivitis. Care should be taken in these tests to check the diagnosis, severity of the disease, presence or absence of corneal involvement and particularly the extent and duration of lymph node enlargement.

NOTE: A second isolation of virus seems to have been effected, and while the second virus has not yet been fully identified with the first, the following three points may be made:

1. The second isolation followed the course of the first in all details.

2. The agent is filtrable through collodion membranes measuring 75 to 100 millimicrons.

3. The serum of patient E. L., source of the first isolation, neutralized the virus obtained from the eye of patient R. H., from whose eye the virus was presumably isolated the second time. The latter's serum also neutralized the virus of the second isolation.

Finally, it should be noted that the present report is a preliminary one and that a general investigation of the two strains which have been isolated will appear elsewhere in greater detail.

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PLACE OF HEMORRHAGIC GLAUCOMA IN ETIOLOGIC CLASSIFICATION OF GLAUCOMA

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In attempting to rectify the common mistake of considering the heterogeneous group of diseases with the common symptom of ocular hypertension as a single disease entity with various stages, I have suggested an etiologic classification of glaucoma [1] based on clinical investigation. One of the diseases included in that classification is listed as hemorrhagic glaucoma, a term which has been applied to the form of glaucoma occurring in eyes with occlusion of the central retinal vein or its tributaries, in which repeated hemorrhages into the anterior chamber are frequently seen. The term should also include glaucoma associated with diabetic rubeosis iridis and perhaps glaucoma following massive retinal hemorrhages and hemorrhages into the vitreous. This paper is submitted to point out the common etiologic factors of this group of conditions and the justification for the term hemorrhagic glaucoma, as well as to indicate its differential diagnosis from other forms of glaucoma which may be present in eyes with retinal venous occlusion, diabetic retinopathy or other severe hemorrhagic vascular disease. Glaucoma with retinal venous occlusion and rubeosis iridis will be discussed separately.

I. OCCLUSION OF THE CENTRAL RETINAL VEIN OR ITS TRIBUTARIES

The classic picture of retinal venous occlusion is usually found in elderly persons with severe angiosclerotic changes and frequently with hypertensive vascular disease. Occasionally, especially in younger patients, it may result from thrombophlebitis. In any case there are slowing of the blood flow in the affected vessels and occlusion by either endothelial proliferation or actual thrombus formation, more frequently the former (Verhoeff [2]). Edema, retinal hemorrhages and exudation

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1. Sugar, H. S.: The Mechanical Factors in the Etiology of Acute Glaucoma, Am. J. Ophth. **24**:851, 1941; The Practical Applications of Gonioscopy to Glaucoma Surgery, ibid. **25**:663, 1942.

2. Verhoeff, F. H.: Obstruction of the Central Retinal Vein, Arch. Ophth. **36**:1, 1907.

from the capillaries along the distribution of the involved dilated veins constitute the typical early picture. The tension is normal or even lower than in the unaffected eye (Moore,[3] Wessely[4]). As time goes on, the edema disappears, leaving yellowish deposits in the retina. The blood is absorbed slowly, and fibrous perivascular sheaths cover the vessel walls. In about 10 to 25 per cent of cases of complete central venous occlusion (Leber[5] 12 per cent, Moore[6] 27.8 per cent, Uhthoff[7] 13 per cent and Gradle[8] 8 per cent), especially those in which there are massive hemorrhages, the tension suddenly becomes elevated about three months after the onset of the occlusion. The glaucoma is congestive in nature; the tension is usually high; the eye is painful and red, and the cornea is edematous. The anterior chamber is normal in depth, unlike that in true acute glaucoma. New vessels form rapidly on the iris surface, and the lens usually becomes cataractous. Sometimes in late stages the lens may become intumescent, thus causing shallowness of the anterior chamber. The normal depth of the chamber of the fellow eye should, however, make the differential diagnosis easy.

This type of glaucoma never occurs with incomplete central venous occlusion, in which the hemorrhages, if present at all, are usually punctate, and only rarely occurs with tributary venous occlusion. Massive retinal hemorrhages might be expected occasionally in the latter, but not in the former.

The cause of the glaucoma has been the subject of considerable controversy. Coats[9] attributed it to blocking of the drainage angle by albuminous exudates arising from the hemorrhages and serum in the vitreous and retina. Inouye[10] and Samuels[11] have shown the presence of albuminous material and extensive vascular membranes in the

3. Moore, R. F.: Medical Ophthalmology, Philadelphia, P. Blakiston's Son & Co., 1922.

4. Wessely, K.: Ueber die Prognose der Thrombose der Zentralvine, Klin. Monatsbl. f. Augenh. **95**:398, 1935.

5. Leber, T., in Graefe, A., and Saemisch, E. T.: Handbuch des gesamten Augenheilkunde, ed. 2, Leipzig, Wilhelm Engelmann, 1915, vol. 2, pt. 2, p. 355.

6. Moore, R. F.: Retinal Venous Thrombosis: A Clinical Study of Sixty-Two Cases Followed over Many Years, London, George Pulman & Sons, Ltd., 1924.

7. Uhthoff: Ber. ü. d. Versamml. d. deutsch. ophth. Gesellsch. **45**:63, 1925.

8. Gradle, H. S.: X-Ray Therapy of Retinal-Vein Thrombosis, Am. J. Ophth. **20**:1125, 1937.

9. Coats, G.: Complete Obstruction of the Central Vein of the Retina, Roy. London Ophth. Hosp. Rep. **16**:262, 1904; Arch. f. Ophth. **86**:341, 1913.

10. Inouye: Roy. London Ophth. Hosp. Rep. **18**:24, 1910.

11. Samuels, B.: Pathologic Changes in Anterior Half of Globe in Cases of Obstruction in Central Vein of Retina, Arch. Ophth. **13**:404 (May) 1935.

chamber angle. These, by obstructing the trabecular spaces, hinder access of the aqueous to Schlemm's canal. Samuels stated well that the glaucoma "could be caused by a change in the metabolism of the eye produced by toxic substances derived from a disintegration of red blood cells and a degeneration of the stroma of the vitreous. It is conceivable that once such toxins had reached the aqueous an adhesive inflammation would be set up, leading to peripheral anterior synechiae." Wood [12] stated the belief that the glaucoma is due to turgescence of the vitreous as a result of absorption of the disintegration products of the hemorrhages. Weinstein [13] also expressed the opinion that the glaucoma is due to swelling of the vitreous, but as a result of accumulation of acid metabolites. Comparison of the depth of the anterior chamber in the two eyes in cases of unilateral hemorrhagic glaucoma by photographic means has led me to conclude that there is no shallowing on the involved side, as would be expected with swelling of the vitreous.

Two statements regarding the etiology of hemorrhagic glaucoma, one by Gradle [8] and the other by Duke-Elder,[14] warrant consideration. Gradle stated that the glaucoma is dependent on "a preglaucomatous state in which the altered intraocular circulation precipitates an acute hypertensive attack. The unaffected eye develops a clinically recognizable compensated glaucoma at a somewhat later date." Duke-Elder likewise contended "that thrombosis frequently occurs in preglaucomatous eyes; the vascular accident may merely precipitate a predestined attack, and indeed, the glaucoma may be a factor in determining the venous obstruction." The last portion of the statement, that glaucoma may be a factor in determining venous obstruction, is true in certain cases, but in the cases of hemorrhagic glaucoma under consideration here the occlusion was primary. Both Gradle and Duke-Elder, in holding that the glaucoma is merely precipitated on a preglaucomatous background, failed to recognize that when hemorrhagic glaucoma occurs in a patient who has or is predisposed to glaucoma simplex, the hemorrhagic glaucoma is of an entirely different nature and is actually a different disease. I am convinced that the venous occlusion and the form of simple glaucoma appearing in a certain number of patients are due to a common factor, namely marked vascular

12. Wood, D. J.: Suggestion as to Cause of Glaucoma Following Thrombosis of Retinal Vein, Brit. J. Ophth. **16**:423, 1932.

13. Weinstein, P.: Pathogenesis of Thrombosis of Central Retinal Vein and of Consecutive Glaucoma, Brit. J. Ophth. **23**:392, 1939.

14. Duke-Elder, W. S.: Textbook of Ophthalmology, St. Louis, C. V. Mosby Company, 1941, vol. 3, p. 2578.

sclerosis. Friedenwald [15] has shown histologically that in some cases, at least, glaucoma simplex is probably due to sclerosis of the afferent vessels to Schlemm's canal. In such cases it may be presumed that similar sclerotic changes are present in the retinal vessels, predisposing to venous occlusion. With the disintegration of the massive hemorrhage and the accumulation of tissue metabolites in the eye, inflammation results in the entire globe, involving also the anterior portion of the uvea and the tissues bounding the chamber angle. Obstruction of the trabecular spaces by fibrinous coagulum or reduction of the osmotic factors by the increase in the proteins of the aqueous may well be the early cause of the glaucoma. In two eyes examined gonioscopically by me early in the course of hemorrhagic glaucoma, an open but highly congested chamber angle was seen. The presence of albuminous fluid could not, of course, be determined gonioscopically. In all other cases of hemorrhagic glaucoma in which the eye was examined by this method, the chamber angle was closed by a vascular membrane. Rupture of the thin-walled vessels comprising this membrane when the tension of the eyeball is reduced suddenly is the reason the eye fails to respond to antiglaucoma surgical procedures.

Clinically, hemorrhagic glaucoma differs from the form of simple glaucoma sometimes seen in the same persons, as well as from other forms of glaucoma. It differs from simple glaucoma in its acute malignant onset with vascular congestion and from true acute glaucoma in that the anterior chamber is of normal depth rather than shallow, as it always is in the last-named condition. It is, then, a definite clinical entity. Its position in the suggested etiologic classification of the group of diseases manifesting glaucoma is shown in table 1.

The occurrence of a form of glaucoma differing in no way from glaucoma simplex in the fellow eye of patients with unilateral hemorrhagic glaucoma following venous occlusion has been reported by Gradle [8] and Moore [6] (2 cases each). In each of Gradle's 2 cases (in which roentgen radiation was not used in treatment), a true "compensated glaucoma" developed in the unaffected eye after the rise of tension had appeared in the eye with venous thrombosis. In 1 of these there was thrombosis of a tributary vein, while the central vein was involved in the second. Of Moore's cases (cases 52 and 54), the tension was 31 mm. of mercury (Schiøtz) in 1 and 40 mm. in the other. In the latter case the tension in the same eye was 22 mm. eleven months later, 32 mm. ten months after that and 100 mm. in five years. Unfortu-

15. Friedenwald, J. S.: Circulation of the Aqueous: V. Mechanism of Schlemm's Canal, Arch. Ophth. **16**:65 (July) 1936.

nately, Moore gave no indication as to the presence or absence of vascular congestion and did not differentiate cases of glaucoma etiologically except to describe some of them as instances of acute glaucoma and a few as instances of chronic glaucoma. He stated that in 7 of his cases "the well-recognized association of the two conditions,

TABLE 1.—*Suggested Etiologic Classification of Glaucoma*

1. Failure of osmotic forces (no mechanical closure of the chamber angle by iris)
   (*a*) Arteriosclerosis (or narrowing) of afferent vessels to Schlemm's canal (Friedenwald)—chronic simple glaucoma
   (*b*) Obstruction of the trabecular spaces
      (1) Glaucoma capsulare
      (2) Pigmentary obstruction—only when a marked deposit is present
      (3) Blocking of trabecular spaces by cellular debris in cases of iridocyclitis, active and healed
      (4) Blocking by tumor growth
   (*c*) Increased protein in the aqueous—severe uveitis
   (*d*) Vascular changes in the angle due to the toxic effect of severe retinal hemorrhage and hemorrhage into the vitreous—hemorrhagic glaucoma (the angle is open early and closed by the iris later)
      (1) Occlusion of central retinal vein
      (2) Diabetic rubeosis
2. Mechanical closure of the chamber angle by the iris
   (*a*) Shallow angle glaucoma
      (1) Acute glaucoma, including the recurrent form which was formerly called "chronic congestive glaucoma" (this type corresponds to the acute and chronic congestive glaucoma of the older classification)
      (2) Acute glaucoma due to intumescence of the lens
      (3) Dislocation of the lens into the anterior chamber
   (*b*) Glaucoma following an operation for cataract—aphakic obstructive glaucoma (in this type the chamber is deep, the angle blocked)
   (*c*) Late hemorrhagic glaucoma
3. Irritation of ciliary processes in cases of posterior dislocation of the lens
4. Lack of communication between the anterior and the posterior chamber
   (*a*) Seclusion of the pupil
   (*b*) Total posterior synechia
5. Obstruction of venous drainage in experimental and in clinical glaucoma following obstruction of the vortex vein and in pulsating exophthalmos
6. General vascular hyperemia—including the hyperemia and changes following concussion (traumatic glaucoma) and the histamine-like reaction of epidemic dropsy.
7. Congenital anomalies
   (*a*) Hydrophthalmos
   (*b*) Juvenile glaucoma
   (*c*) Glaucoma associated with nevus flammeus or with neurofibromatosis

venous thrombosis and glaucoma, was unmistakable . . . but there were three where the association was different, in that the other eye, at the time that advice was sought about the eye with the thrombosis, was already the seat of the glaucoma." He concluded that in some cases of obstruction to the outflow of the retinal veins "after many years a very insidious form of slowly progressive glaucoma ensues, whilst in others actual thrombosis of the central vein occurs, and then the well known risk of acute glaucoma arises." He found it difficult to explain

this insidious form of glaucoma developing after venous obstruction in the opposite eye but thought it most likely "that these cases have some abnormal formation of the disk, perhaps of congenital origin, with which an abnormal ending of the vein is concerned, which results in an obstructed venous outflow, and the ultimate result of this combination after many years is a very insidious glaucoma." Moore, then, stated the belief that both types of glaucoma, the hemorrhagic and the simple, in these cases was due to venous obstruction whether such obstruction was apparent or not.

Nine patients with retinal venous occlusion associated with ocular hypertension were studied by me in the glaucoma clinic of the Illinois Eye and Ear Infirmary. Three had hemorrhagic glaucoma; 1 of these had an increased tension in the other eye. The other 6 patients, all

TABLE 2.—*Cases of Retinal Venous Occlusion Associated with Ocular Hypertension*

Case	Highest Preoperative Tension (Mm. Hg Schiøtz)		Central or Tributary Vein Involved
	Right Eye	Left Eye	
1	43 (simplex)	42 (simplex)	Left tributary vein
2	44 (simplex)	Normal	Left tributary vein
3	30.5 (simplex)	Normal	Left central vein, incomplete
4	28	37 (simplex)	Right tributary vein
5	82 (hemorrhagic)	32 (simplex)	Right central vein, complete
6	30.5 (only once)	33.5 (simplex)	Right central vein, incomplete
7	20	41 (simplex)	Right tributary vein
8	60 (hemorrhagic)	Normal	Right central vein, complete
9	23	82 (hemorrhagic)	Left central vein, complete

with unilateral venous occlusion, had glaucoma of the simplex type, 5 in the fellow eye only and 1 in both eyes (table 2).

CASE 1.—A 44 year old Negro man was seen in April 1937, when he was found to have occlusion of the left superior retinal vein. His blood pressure was 200 mm. systolic and 130 diastolic. The anterior chambers were of normal depth. The ocular tension was 25 mm. on the right and 32 mm. on the left. There was no evidence of vascular congestion. Pilocarpine nitrate in 2 per cent solution was ordered four times daily for both eyes. The subsequent course of the tension, as shown in chart 1, indicated that the patient had bilateral glaucoma simplex. The chamber angles were entirely normal. An iridencleisis was done on the left eye on August 27 and a trephining on the right eye on Feb. 24, 1940. The retinal vessels were severely sclerosed.

CASE 2.—A 53 year old Negro man was first seen in January 1939 with an occlusion of the left inferior retinal vein. His blood pressure was 205 mm. systolic and 130 mm. diastolic. The anterior chambers were of normal depth. The ocular tension was 38 mm. on the right and 21 mm. on the left. The course of the tension of the right eye is shown in chart 2. The tension was never elevated in the left eye. (The patient was observed until Nov. 13, 1941.) Both chamber angles were entirely normal.

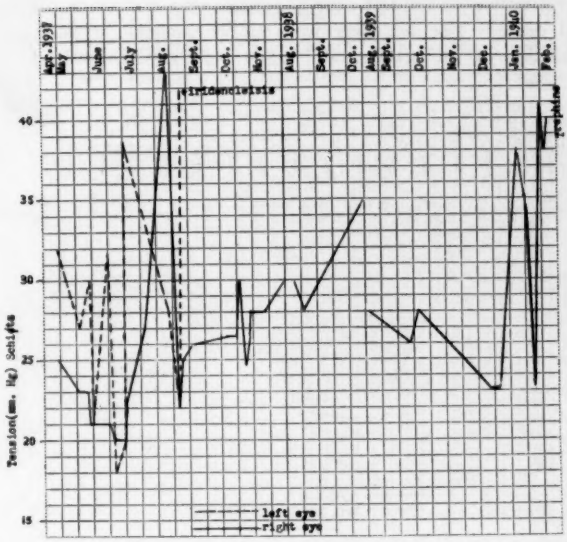

Chart 1 (case 1).—Course of the tension in both eyes.

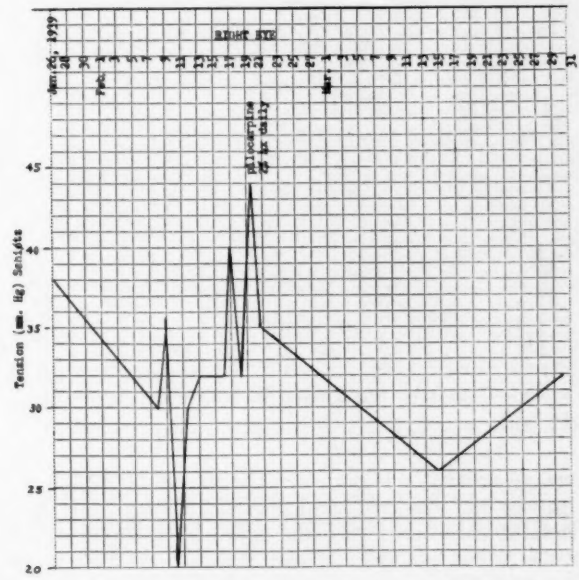

Chart 2 (case 2).—Course of the tension in the right eye.

CASE 3.—A 48 year old white man was seen in January 1940, when a diagnosis of incomplete obstruction of the left central retinal vein was made. Both chambers were of normal depth. The left disk was poorly outlined, with engorgement of the veins, attenuation of the arteries and many punctate hemorrhages in the pos-

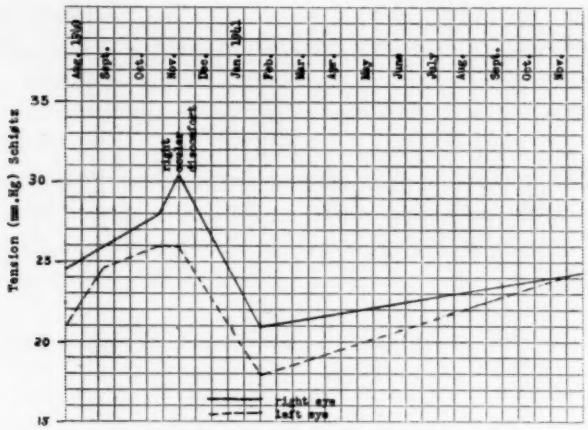

Chart 3 (case 3).—Course of the tension in both eyes.

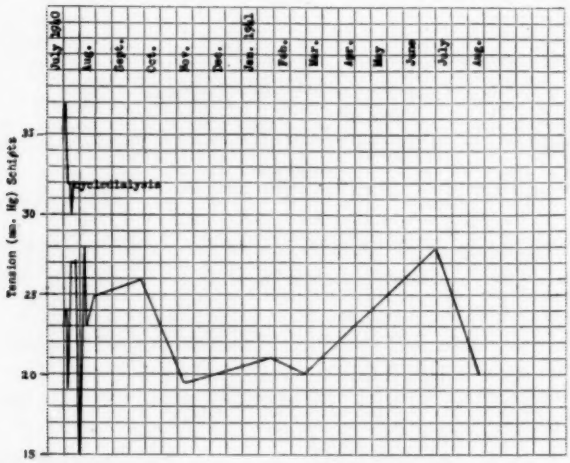

Chart 4 (case 4).—Course of the tension in both eyes (upper curve, left eye; lower curve, right eye).

terior pole. A central scotoma was present. The tension of the left eye remained normal. (The patient was observed until Nov. 29, 1941.) The tension of the right eye was elevated only once, when the patient complained of discomfort in that eye. Since the patient was seen at that time and the tension verified, this case history was included (chart 3). Both chamber angles were entirely normal.

CASE 4.—A 71 year old Negro man was seen in July 1940 with an occlusion of the right inferior temporal retinal vein. The anterior chambers were of normal

depth. The ocular tension was 23 mm. on the right and 35 mm. on the left. The course of the tension is shown in chart 4. The tension in the right eye was never found to be over 28 mm. (The patient was observed until Nov. 18, 1941.) There was never any evidence of congestion. The chamber angles were entirely normal.

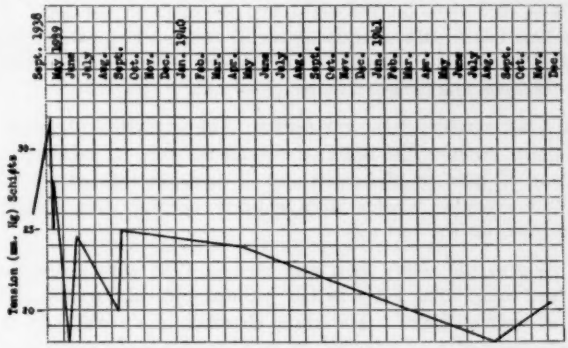

Chart 5 (case 5).—Course of the tension in the left eye.

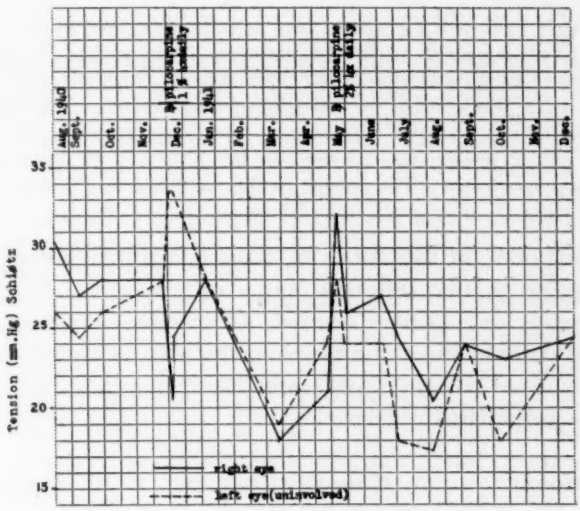

Chart 6 (case 6).—Course of the tension in both eyes.

CASE 5.—A 72 year old white man was seen in January 1939 because of severe pain and redness of his right eye. The vision in this eye had suddenly become poor four months earlier. The ocular tension was 82 mm. on the right and 26 mm. on the left. Both chambers were of normal depth. There were visible new-formed vessels around the right pupillary border. The right chamber angle was completely closed by vascularized tissue. The left was entirely open and normal in appearance. The right lens was cataractous. The right eye was trephined and later enucleated when trephining failed to influence the tension. On May 6 pilo-

carpine nitrate in 2 per cent solution was ordered for instillation into the left cul-de-sac four times daily, but the tension of the left eye was 32 mm. three days later. The subsequent course with pilocarpine is shown in chart 5.

CASE 6.—A 67 year old Negro man was seen in August 1940 with incomplete occlusion of the right central retinal vein. The blood pressure was 210 mm. systolic and 110 mm. diastolic. The anterior chambers were of normal depth. The ocular tension was 30.5 mm. on the right and 26 mm. on the left. The tension of the right eye was never subsequently above 28 mm. (The patient was observed until March 12, 1941.) The course of the tension of the left eye is shown in chart 6. Both chamber angles were entirely normal.

CASE 7.—An elderly white man was seen in August 1939 with occlusion of the right superior retinal vein. The anterior chambers were of normal depth. The ocular tension was 20 mm. on the right and 41 mm. on the left. No congestion was present. Both chamber angles were entirely normal. An Elliot trephining was successfully done on the left eye.

CASE 8.—A 70 year old white man was seen in 1938 with an occlusion of the right central retinal vein. The eye was red, painful and cataractous. The anterior chambers were of normal depth. The right chamber angle was closed by a vascular membrane. The left was normal. New-formed vessels were present on the right iris. The tension of the right eye was 60 mm. and that of the left remained normal. The patient had been seen several months earlier at the Cook County Hospital, where a diagnosis of retinal venous occlusion had been made.

CASE 9.—A 74 year old white man was seen in July 1940 with occlusion of the left central retinal vein of six weeks' duration. The eye had become red and painful about three weeks after the onset. The anterior chambers were of normal depth. The left iris was covered by new-formed blood vessels. The left chamber angle was closed by a vascular membrane. The blood pressure was 135 mm. systolic. The ocular tension was 23 mm. on the right and 82 mm. on the left. The left eye was enucleated. The tension of the right eye was never found to be elevated. The right chamber angle was entirely normal.

The observations in this series of cases uphold the contention that one is dealing with two different forms of glaucoma, of which one probably depends on vascular sclerosis (glaucoma simplex type) and the other on the toxic effect of massive intraocular hemorrhage (hemorrhagic glaucoma). No cases of hemorrhagic glaucoma in eyes with tributary vein thrombosis occurred.

II. HEMORRHAGIC GLAUCOMA ASSOCIATED WITH DIABETIC RUBEOSIS IRIDIS

Hemorrhagic glaucoma which occurs in certain diabetic patients with rubeosis iridis is comparatively rare. It was first described by Salus [16] in 1928. It apparently occurs only in cases in which there are repeated large intraocular hemorrhages. Like the hemorrhagic glaucoma following retinal venous occlusion, it is characterized by new-formed vessels on

16. Salus, R.: Rubeosis iridis diabetica eine bisher unbekannte diabetische Irisveränderung, Med. Klin. **1**:256, 1928.

the iris surface and in the chamber angle, closing the latter. It is likely that occasional cases occur in which the toxic effect of the disintegrating blood is less marked and the formation of some new-formed iris vessels may even antedate the glaucoma for a time. Kurz[17] in 1939 first described the appearance of the chamber angle in this condition. Clinically this form of glaucoma is exactly like that following retinal venous occlusion.

Etiologically, the two types of hemorrhagic glaucoma are the same, both being associated with massive intraocular hemorrhages based on severe angiosclerotic changes. Both also may be found in patients with typical glaucoma simplex involving the fellow eye (case 12). Both longitudinal and cross sections of the optic nerve and sections of the globe in case 10 failed to reveal any evidence of central venous occlusion, although severe angiosclerosis was present.

CASE 10.—A 69 year old white man, a private patient of Dr. H. S. Gradle and Dr. S. J. Meyer, was first seen by the former in 1924, when his corrected vision was 20/15 in each eye. In 1935 the vision was reduced to 20/50 in the right eye and 10/100 in the left corrected. Retinal angiosclerosis and diabetic retinopathy were present in each eye. There was no evidence of glaucoma. In May 1937, when the patient was seen by me, his vision was reduced to counting of fingers with both eyes. The eyes were red and painful. The ocular tension was elevated, and many new-formed blood vessels were present on the irises. Repeated hemorrhages into the anterior chamber occurred both before and after trephining of the right eye, which was unsuccessful in reducing the tension. An enucleation of the right eye was done in February 1939. The report of the Army Medical Museum (accession no. 64143) follows: "The corneal epithelium is irregular and in places separated from the stroma by a zone of fibrous tissue which contains dilated blood vessels and infiltrating round cells. There is a central ulcer with sloughing and apparent perforation. The iris is widely adherent to the cornea, almost obliterating the anterior chamber. Granulation tissue fills the pupillary area. Blood appears in the posterior chamber and in the vitreous. Hemorrhages are found in the retina, several being subhyaloid. Hyaline sclerosis has almost occluded some of the larger retinal arteries. There is also hyaline sclerosis of the arterioles. Organizing blood appears on the surface of the disk. There is thickening of the arterioles in the choroid. The lamina cribrosa is bowed backward. There is some gliosis of the optic nerve. The blood vessels in the optic nerve are not shown in cross section but those visible are patent." Subsequent longitudinal and cross sections failed to reveal obstruction in the central retinal vein.

CASE 11.—An elderly diabetic patient with bilateral hemorrhagic glaucoma was seen by me in 1940. The eyes were blind, red and painful. The anterior chambers were of normal depth. The irises were covered by new-formed blood vessels, which also closed the chamber angles.

CASE 12.—A 49 year old white diabetic woman was seen in January 1941. She had noted gradual loss of vision in both eyes during the previous two or three years. Two or three days before admission her right eye had become red and painful. The vision in the right eye was reduced to ability to see hand move-

17. Kurz, O.: Zur Rubeosis iridis diabetica, Arch. f. Augenh. **110**:284, 1937.

ments at 1 foot (30 cm.). The vision in the left eye was reduced to counting fingers at 2 feet (60 cm.). The ocular tension was 80 mm. on the right and 15 mm. on the left. The right eye was congested, with the anterior chamber normal in depth. New-formed blood vessels were present on the anterior surface of the iris. The chamber angle was obscured by hemorrhage. The left eye had a normal chamber angle and depth. This eye showed diabetic retinopathy and a deep glaucomatous cup associated with changes in the visual field typical of chronic simple glaucoma.

CONCLUSIONS

1. The term hemorrhagic glaucoma is appropriate for the form of glaucoma following retinal venous occlusion and for that associated with diabetic rubeosis iridis, since both conditions are due to the inflammatory changes resulting from disintegration and absorption of repeated large intraocular hemorrhages.

2. The clinical pictures of the two types of glaucoma warrant their inclusion under the same heading.

3. Hemorrhagic glaucoma is a different entity from the form of simple glaucoma which is found in the fellow eye of some of the patients. Vascular sclerosis is probably the common background both for the intraocular hemorrhages which lead to hemorrhagic glaucoma and for the glaucoma simplex, which is very likely due to angiosclerotic changes in the afferent vessels to Schlemm's canal. This fact is suggestive clinical support of Friedenwald's histologic evidence for the arteriosclerotic causation in at least a portion of the cases of glaucoma simplex.

Dr. H. S. Gradle and Dr. S. J. Meyer gave permission for the use of case 10, and Mrs. Georgia Brader, medical social worker of the glaucoma clinic, Illinois Eye and Ear Infirmary, assisted in the gathering of material.

Barnes General Hospital.

ACETYLCHOLINE IN OPHTHALMOLOGY AND THE TREATMENT OF OCULAR PAIN

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ACETYLCHOLINE IN OPHTHALMOLOGY

Acetylcholine was first prepared in 1867 by Baeyer,[1] but it was not until 1906 that Hunt and Taveau [2] discovered its action on the circulation. Another twenty years passed before the drug was clinically investigated by Villaret and Justin-Besançon;[3] I believe it was first used by them in 1926 in a case of Raynaud's disease. During the next fifteen years it was widely used in France, and like most new medicines it went through an initial period when it was tried in the treatment of various diseases and a second one when the boom was over and when experience had shown in what diseases and in what selected cases it could be helpful.

Pharmacodynamics.[4]—Acetylcholine derives from choline and is normally found in many tissues of the body, as it is liberated at the nerve endings in vagal or parasympathetic nerve impulses. Inversely, the injection of acetylcholine will produce changes similar to those obtained by stimulation of the vagal or the parasympathetic nerves and antagonistic to those obtained through epinephrine. To a great extent

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* Not in practice.

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1. Baeyer: Ann. d. Chem. **142**:325, 1867; cited by Alles.[4e]

2. Hunt, R., and Taveau, R. de M.: On the Relation Between the Toxicity and Chemical Constitution of a Number of Choline Derivatives, Brit. M. J. **2**:1788, 1906.

3. Villaret, M., and Justin-Besançon, L.: The Therapeutical Applications of Acetylcholine, Lancet **1**:493, 1929; The Therapeutic Use of Acetylcholine, M. J. & Rec. **132**:35, 1930. Villaret, M.: Étude critique sur l'emploi des éther-sels de la choline, Presse méd. **39**:601, 1931.

4. (*a*) Villaret, M.; Justin-Besançon, L.; Schiff-Wertheimer (Mme.), and Gallois, J.: Les esters de la choline en ophtalmologie, Arch. d'opht. **49**:129, 1932. (*b*) Dainow, I.: Action pharmacodynamique de l'acétylcholine, Rev. méd. de la Suisse Rom. **51**:520, 1931. (*c*) Gaddum, J. H., in Luck, J. M.: Annual Review of Biochemistry, Stanford University, Calif., Stanford University Press, 1935, vol. 4, p. 311. (*d*) Duggan, W. F.: Acetylcholine in the Treatment of Retrobulbar Neuritis, Arch. Ophth. **17**:579 (April) 1937. (*e*) Alles, G. A.: The Physiological Significance of Choline Derivatives, Physiol. Rev. **14**:276, 1934.

acetylcholine was used long before physicians knew it, since one of the reasons for the action of physostigmine is that it blocks the normally rapid destruction of the acetylcholine formed in the tissues.[5] The physiologic activity of acetylcholine, which is often called the vagal hormone, may be summarized as follows, at least in relation to ophthalmology:

Capillaries: No action and therefore no flushing of the face.

Peripheral Arteries and Arterioles: At first a slight contraction, then a dilatation which begins after five or ten minutes and reaches its maximum after half an hour. This can usually be seen with the ophthalmoscope or by means of endoscopy.

Blood Pressure: A slight drop, but more moderate than with drugs which also dilate the capillaries.

Ocular Tension: No action or sometimes a slight increase.

In France there are two proprietary medicines generally used. Both contain acetylcholine chloride. At first there was some difficulty in obtaining a stable aqueous solution and the drug came in the form of a white crystallized powder which was dissolved in water at the time of injection, but for several years a stable aqueous solution containing acetylcholine chloride and anhydrous dextrose has been available. There seems to be no necessity for gradually increasing the dose, and the toxicity is low. The safety margin is about 1/20. I have injected without bad effect up to 0.8 Gm. daily, whereas the usual amount is 0.05 to 0.2 Gm. daily. If there is any danger in the use of acetylcholine it is due not to its toxicity but to its action on the circulation. It is for that reason that it should be handled with care, at least in the treatment of older persons.

Acetylcholine is administered subcutaneously or intramuscularly but never intravenously. It is prepared in ampules containing 0.1 or 0.2 Gm. of acetylcholine chloride. One can also obtain it combined with camphor or with a salt of yohimbine, sparteine or papaverine. The first of these combinations is not used in ophthalmology, as yohimbine prevents the dilatation of the arteries, but since it lowers the blood pressure it has been advocated in the treatment of cerebral hemorrhage. Acetylcholine and sparteine (0.1 Gm. of acetylcholine and 0.05 Gm. of sparteine sulfate) dilates the arterioles, lowers the blood pressure and stimulates the heart. It is used for diseases of the heart and circulation but only seldom in ophthalmology. I have found acetylcholine and camphor (0.1 Gm. of acetylcholine chloride and 0.2 Gm. of camphor) useful. I prefer it to pure acetylcholine, particularly in the treatment of old

5. Best, C. H., and Taylor, N. B.: Physiological Basis of Medical Practice, ed. 3, Baltimore, William Wood & Company, 1937, p. 1513.

persons and when there is marked arteriosclerosis, because in these instances a drop in the blood pressure is often the cause of new accidents. Besides, the action of camphor is not thoroughly understood, and some investigators claim that in addition to stimulating the heart it facilitates the flow of blood. The acetylcholine and papaverine combination is particularly efficacious against spasm.

Indications for the Use of Acetylcholine.[6]—Acetylcholine is particularly useful in the treatment of disturbances caused by a vasoconstrictor spasm of the arteries in the retina or the optic nerve.[7] Such a spasm can have many different causes, for example, tobacco, alcohol,[8] quinine,[9] ethylhydrocupreine (optochin) hydrochloride, pentavalent arsenic [10] and phenobarbital.[11] As Duggan [4d] has pointed out, in many cases so-called retrobulbar neuritis may be the result of a vasoconstrictor spasm, and the loss of vision sometimes following repeated hemorrhages is probably due to the same cause.[12] In all such instances good results have been reported with the use of acetylcholine.

One of the most interesting observations is that of Hudelo.[13] He saw his patient half an hour after complete loss of vision in one eye. All the retinal arteries were empty and white. Hudelo injected 0.2 Gm. of acetylcholine chloride and examined the fundus every three minutes for the next hour. After the first three minutes the blood had returned in the arteries just beyond the margins of the disk, and then it gradually crept to the periphery within an hour. Vision was 20/100 after forty minutes. After one hour Hudelo gave his patient some amyl nitrite. Vision was 20/70 the next day, 20/40 after a week and 20/25 a month later. One interesting point is that whereas that part of the retina which

6. (*a*) Margerin, R., in Bailliart, P.; Coutela, C.; Redslob, E., and Velter, E.: Traité d'ophtalmologie, Paris, Masson & Cie, 1939, vol. 8, pp. 25 and 82. (*b*) Villaret, Justin-Besançon, Schiff-Wertheimer and Gallois.[4a]

7. de Saint Martin, R.: L'acétylcholine dans les angiospasmes rétiniens, Ann. d'ocul. **168**:102, 1931.

8. Bonnefon: L'acétylcholine dans le traitement de l'amblyopie toxique alcoolique, Prat. méd. franç. (no. 2 bis) **12**:65, 1931.

9. (*a*) Hartmann, E.: Quelques exemples d'effets heureux de l'acétylcholine, Bull. Soc. d'opht. de Paris, 1933, p. 414. (*b*) Hartmann, E., and Voisin, J.: Amaurose quinique traitée par l'acétylcholine, ibid., 1934, p. 54.

10. Mawas, J., and Pinheiro, F.: Cécité rapide au cours d'un traitement par la tryparsamide, guérison par l'acétylcholine-pilocarpine, Bull. Soc. d'opht. de Paris, 1936, p. 336.

11. Magitot, A., and Offret, G.: Troubles visuels et hypertension artérielle rétinienne dans une intoxication quinique et une intoxication barbiturique, Bull. Soc. d'opht. de Paris, 1936, p. 163.

12. Hartmann, E., and Parfonry, J.: Cécité par perte de sang améliorée par l'acétylcholine, Bull. Soc. d'opht. de Paris, 1934, p. 56.

13. Hudelo: Spasme du tronc de l'artère centrale de la rétine, Bull. Soc. d'opht. de Paris, 1939, p. 14.

received its normal blood supply again within forty minutes returned entirely to normal, the rest of the fundus about a tortnight later had developed the very image which is found in pigmentary degeneration of the retina. This tends to show how long the retina can survive without a blood supply and also that a circulatory deficiency is probably the cause of pigmentary degeneration.

Vasoconstriction of the posterior cerebral artery is also likely to respond well, and acetylcholine when injected early can sometimes stop an ophthalmic migraine or an attack of temporary hemianopia.[14]

Spasmodic vasoconstriction is the major indication for acetylcholine, and in the treatment of young patients with healthy arteries doses to 0.2 Gm. of acetylcholine chloride per injection and 0.8 Gm. per day can be used with safety.

Another indication for acetylcholine is the presence of a superimposed spasm on chronic endarteritis. One of my first experiences with acetylcholine was in a case of syphilitic arteritis of the upper retinal artery partially obstructing the lumen, with a sudden and complete spasmodic block. The spasm was relieved at once with 0.1 Gm. of acetylcholine chloride, and it did not recur while the patient received the same daily dose together with an antisyphilitic treatment which cured the arteritis.[9a] Acetylcholine can of course not cure the organic lesion, but by eliminating the additional functional impairment to the circulation it sometimes allows the necessary time to treat and cure the arteritis.

In diseases of the eye in which there is no spasmodic vasoconstriction but a permanent and progressive narrowing of the arteries through angiosclerosis, the use of acetylcholine is more questionable. Some good results have been reported in circinate retinitis [15] and in senile degeneration of the macula, but as a rule there is no improvement and I am rather diffident about using this medication in treating old persons with narrow and hard arteries. Not that I have ever seen a blood vessel rupture, but it is sometimes only under a fairly high pressure that the blood is forced through such arteries, and a sudden drop is apt to bring new deficiencies in the circulation, for example a softening of the brain. In the treatment of such persons one should inject only small doses of acetylcholine chloride at first (0.05 Gm.) and gradually increase the amount while watching the blood pressure. According to my experience it is best to use the acetylcholine-camphor combination.

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14. Dejean, C.: Migraines ophtalmiques et acétylcholine, Presse méd. **40**:1950. 1932. Hartmann.[9a]

15. Redslob, E.: Le traitement de la rétinite circinée, Bull. Soc. d'opht. de Paris, 1934, p. 119.

Use of acetylcholine is advisable when an artery is obstructed by an embolism [16]; sometimes the clot is thus allowed to travel farther and only block one branch of the artery. Another reason is that a great part of the trouble is due to the vasoconstrictor spasm which is always present; I shall discuss this later. It is also on account of the associated arterial vasoconstriction that acetylcholine has sometimes proved useful in the treatment of thrombosis of the retinal veins.[17] Michaux,[18] who has published some particularly good results, used a retrobulbar injection of 0.05 to 0.1 Gm. of acetylcholine chloride every three days and a subcutaneous injection of cobra venom every five days, the latter being also supposed to dilate the small arteries.[19]

On the ground that optic nerve atrophy might be due in some cases to prolonged vasoconstriction,[7] acetylcholine has been tried in the treatment of this condition. One can hardly expect much, but some improvement has been reported (in cases of quinine poisoning several years earlier,[20] of malaria [21] and of tabes [6a]). Acetylcholine has also been tried in the treatment of diseases for which it was suspected that an insufficient blood supply was responsible. I have seen some slight improvement in cases of optic nerve atrophy with cupping and contracted fields. In pigmentary degeneration of the retina acetylcholine seems to me of no avail, but Moreu [22] has reported good results after injecting acetylcholine chloride into the vitreous. Redslob,[23] who experimented on the rabbit, injected 0.005 Gm. of acetylcholine chloride into the

16. Villard, H.; Dejean, C., and Temple, J.: Trois cas d'embolie de l'artère centrale de la rétine, rôle du spasme artériel surrajouté, Arch. d'opht. **49**:72, 1932.

17. Schiff-Wertheimer, S.: Obstruction partielle de l'artère centrale de la rétine traitée par l'acétylcholine, Bull. Soc. d'opht. de Paris, 1929, p. 86. Terrien, F., in discussion on Schiff-Wertheimer. Terson, A., in discussion on Hartmann.[9a] Villaret and Justin-Besançon.[4a]

18. Michaux, P.: Traitement des obstructions des vaisseaux rétiniens par injection rétro-bulbaire d'acétylcholine suivies d'injections intra-musculaires de vénin de cobra, Bull. Soc. d'opht. de Paris, 1938, p. 605.

19. Bailliart, P., and Koressios, N. T.: Quelques effets du vénin de cobra sur l'oeil, Bull. Soc. d'opht. de Paris, 1934, p. 240.

20. Bollack, J., and Autier: Altérations du champ visuel par intoxication quinique ancienne, ses modifications par l'acétylcholine, Bull. Soc. d'opht. de Paris, 1928, p. 564. Worms, G., and Pinelli: Grave altération du champ visuel d'origine quinique traitée avec succès par l'acétylcholine, ibid., 1930, p. 15.

21. Sedan, J., and Jayle, G.: Spasmes de l'artère centrale de la rétine, Ann. d'ocul. **173**:632, 1936.

22. Moreu, A.: Consideración sobre la patogenia y tratamiento de la degeneración pigmentaria della rétina, Arch. de oftal. hispano-am. **33**:653, 1933.

23. Redslob, E.: Sur la possibilité d'une application locale de l'acétylcholine dans le traitement des spasmes des artères rétiniennes, Bull. Soc. d'opht. de Paris, 1930, p. 143.

vitreous and saw a marked dilatation of all the arteries which lasted more than twenty-four hours. He also observed a lowering of the ocular tension, which he attributed to the acidity of the liquid injected into the vitreous: The solution he used had a p_H of 2.5. Theoretically, acetylcholine does not seem advisable in the treatment of glaucoma, since it tends to raise the ocular tension.[4a] However, the tension is not the only symptom to be considered, and in some cases in which the tension was well controlled by pilocarpine hydrochloride good results were obtained by improving the circulation of the retina and the optic nerve.[24] The fields are sometimes enlarged. I have noted a few such cases,[9a] but acetylcholine should not be considered a routine treatment for glaucoma.

In France there is a proprietary medicine containing pilocarpine and acetylcholine chloride which was being experimented with when the war broke out. Monbrun, who has used it for over two years, told me he had seen it bring about some slight improvement in tabetic optic nerve atrophy and in optic nerve atrophy with cupping. It is at any rate harmless.

RETROBULBAR INJECTIONS OF PROCAINE HYDROCHLORIDE IN THE TREATMENT OF VASCULAR DISEASES OF THE RETINA

As I have already mentioned, acetylcholine is often used in cases of thrombosis of the retinal veins and of obliterating endarteritis or embolism of the retinal arteries, but in such cases I prefer a retrobulbar injection of procaine hydrochloride. I believe Bailliart [25] was the first to advise this treatment, and it undoubtedly sometimes gives a good result. There is great uncertainty, however, as to just how it acts. Bailliart questioned whether the irritation of the retrobulbar tissues does not release histamine; he also mentioned that when injected without epinephrine hydrochloride, procaine hydrochloride is a vasodilating drug. I believe there is a different explanation and that one should turn for it to the work of Leriche and his associates during the last twenty years on the surgical treatment of the veins and arteries. They have taught that when the lumen of an artery or of a vein is obstructed not only are the consequences mechanical, but nervous changes come into play which are at least as important: Any irritation of the inner

24. Villaret, Velter and Oswalt: Glaucome chronique traité par l'acétylcholine et la pilocarpine, Bull. Soc. d'opht. de Paris, 1930, p. 236. Gallois, J.: Acétylcholine dans un cas de glaucome chronique, ibid., 1930, p. 811. Bidault: Le traitement médical général du glaucome, ibid., 1937, p. 446.

25. Bailliart, P.: Le traitement local des affections vasculaires du fond d'oeil, Bull. Soc. d'opht. de Paris, 1938, p. 451.

surface of a vein or of an artery effects a reflex vasoconstriction of all the arteries in the corresponding area, and such a reflex can be started either by a clot acting as an intravascular foreign body or by obliterative endarteritis or endophlebitis.[26]

The fact that such a reflex causes a great part of the symptoms when the blood vessel involved is in the arm or the leg seems fairly well proved. In phlebitis of the leg the edema diminishes rapidly when procaine hydrochloride is injected into the lumbar portion of the sympathetic chain,[27] and if an artery is obstructed the collateral circulation is greatly improved after resection of the obliterated segment.[26] In both instances the vasoconstrictor impulses are blocked, either by interruption of the reflex arc or by removal of the irritation which produced the afferent impulses.

I feel that a similar explanation applies to the eye and that if improvement follows the retrobulbar injection of procaine hydrochloride it is because of the physiologic section of the afferent pathway. Such injections should of course be repeated daily, and no epinephrine hydrochloride should be added.

I have purposely been rather vague and have spoken only of "the afferent pathway," for it is difficult to know along what nerve fibers the afferent impulses travel. It is doubtful that they are somatic, since no such fibers seem to originate from the blood vessels and since the irritation of the veins and arteries gives no impression of pain. As to nerve fibers of the involuntary system, the controversial question of afferent sympathetic fibers is raised. It is not even clear whether the vasoconstrictor impulses are reflected from the ciliary ganglion or from involuntary centers in the brain stem and spinal cord.

RELIEF FROM OCULAR PAIN

The preceding section shows the important consequences that may derive from the severance of the sensory pathway. It is of course in cases of painful disease of the eye that this is most useful, but relief from

26. (*a*) Leriche, R.: La chirurgie de la douleur, Paris, Masson & Cie, 1937, p. 199; (*b*) The Surgery of Pain, translated by A. Young, Baltimore, Williams & Wilkins Company, 1939, p. 240. (*c*) Leriche, R., and Fontaine, R.: Les spasmes vasculaires des membres; Journées internationales périodiques de cardiologie (Royat), Clermont-Ferrand, France, Imprimeries de l'Avenir, 1937, p. 259. (*d*) Leriche, R.: Arteriectomy in Arterial Obliterations, in Matas Birthday Volume, New York, Paul B. Hoeber, Inc., 1931, p. 55. (*e*) Leriche, R., and Stricker, P.: L'artériectomie dans les artérites oblitérantes, Paris, Masson & Cie, 1933.

27. Leriche, R., and Kunlin, J.: Traitement immédiat des phlébites post opératoires par infiltration novocaïnique du sympathique lombaire, Presse méd. **42**:1481, 1934.

pain can in such cases also be obtained through action on the sphenopalatine ganglion and the neighboring nerve fibers.

Anesthesia of Meckel's Ganglion.—Anesthesia of Meckel's ganglion will usually cause some relief in painful ocular diseases, but it is difficult to ascertain just how, as no somatic sensory fibers from the eye are known to travel through the sphenopalatine fossa. It is most likely that one interferes with sympathetic fibers, possibly only efferent vasomotor fibers.

Magitot [28] has advised injecting procaine hydrochloride through the greater palatine foramen and canal, but this does not seem advisable, as the palatine artery may be injured, with consequent loss of the posterior upper molars. A safer method of anesthetizing the sphenopalatine ganglion is the application of a cotton pledget soaked in Bonain's solution (equal parts of cocaine hydrochloride, menthol and phenol) against the pterygopalatine fossa above and behind the middle turbinate.[29]

There is often marked relief, and unexpectedly this sometimes is followed by improvement in the ocular disease causing the pain. This fact has led to the use of this treatment in many cases of painful disease of the anterior segment, and it seems to be particularly useful in cases of scleritis and episcleritis and in most cases of superficial lesions of the cornea with tearing and photophobia, for instance marginal ulcer or trachoma with corneal complications.[28]

Retrobulbar Injections of Alcohol.[30]—A retrobulbar injection of procaine hydrochloride will interrupt the sensory fibers in or near the ciliary ganglion and relieve pain for a few hours. A more lasting effect is obtained when alcohol is used.

When there is no vision and no hope of restoring any, for example in absolute glaucoma, one can use an injection of 80 to 95 per cent alcohol. When the vision is good or can be expected to improve such an injection is inadvisable, as it might injure the optic nerve. But if a weaker percentage is used (40 to 45 per cent) there is no danger. Weekers,[31] of Liége, apparently was the first to use this treatment, and

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28. Magitot, A.: La douleur oculaire, Ann. d'ocul. **174**:361, 1937.

29. Dubois-Poulsen, A.: Le ganglion sphéno-palatin, Ann. d'ocul. **174**:217, 1937. Thurel, R.: La phénolisation du ganglion sphéno-palatin, Arch. d'opht. **2**:506, 1938.

30. (*a*) Weekers, L.: Traitement de l'hypertension oculaire compliquant les iridocyclites, Arch. d'opht. **53**:166, 1936; (*b*) Traitement des affections oculaires par les injections orbitaires d'alcool, Ann. d'ocul. **176**:81, 1939. (*c*) Magitot.[28]

31. Weekers, L.: Traitement des yeux douleureux et doués de vision par l'injection orbitaire d'alcool peu concentré, Arch. d'opht. **47**:299, 1930; Réactions ophtalmologiques expérimentales provoquées par l'injection orbitaire de diverses substances, ibid. **48**:321, 1931.

for some time he had few followers because of the fear of damaging the optic nerve even with a weak solution. After more than ten years of experience and many hundred of injections, however, one must admit that the views he expressed as far back as 1930 are correct and that such injections are both useful and harmless. One can even use a slightly stronger percentage without danger, up to 50 or 55 per cent, as the alcohol is diluted by the preceding injection of procaine hydrochloride. The technic is simple: 1 cc. of a 2 or 4 per cent solution of procaine hydrochloride is injected behind the eye in the region of the ciliary ganglion, the needle is left in place and two or three minutes later 1 to 1.5 cc. of alcohol is injected. The injection is not painful. When the execution is good there should be no oculomotor paresis but only corneal anesthesia for a few days. When the alcohol has not been injected near the ciliary ganglion but more externally there may be a paralysis of the lateral rectus muscle for a few weeks. When the injection has been correctly given the only complications are some edema of the lids with slight exophthalmos for a week or so and mydriasis, which is sometimes a little more persistent. It is curious to notice that, whereas the corneal sensitivity returns within three or four days, the pain does not for two or three weeks. When it does there is no objection to a second injection.

Relief from pain is not the only indication. Weekers [30a] expressed the belief that these injections are the best treatment for inflammatory glaucoma secondary to iridocyclitis, and I agree with him. The drop in tension is not always immediate, however, and may only be found after twenty-four or forty-eight hours. Strangely enough, the course of the iridocyclitis in certain cases seems to be favorably influenced. Magitot [28] has advised these injections in all cases of painful iritis, even when there is no increase of ocular tension, and the results are often good. I have seen some particularly favorable ones in gonococcic iritis, which is often so painful.[32] Magitot has gradually used this treatment more and more for all painful diseases of the anterior segment, with good effect on the pain always and even on the causal disease sometimes. He stated the belief that it is advisable in many cases of keratitis with marked photophobia and particularly in cases of phlyctenular keratitis and syphilitic interstitial keratitis.[33] In both of these diseases the course of the keratitis is shortened, but of course the injection of alcohol does not replace but accompanies the usual treatment.

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32. Magitot, A., and Morax, P.: Action curatrice des injections intra-orbitaires d'alcool dans quelques cas d'iritis gonococciques, Bull. Soc. d'opht. de Paris, 1937, p. 617.

33. Magitot.[28] Weekers.[30b]

It is naturally surprising that one should observe these improvements, and it is difficult to understand how they are brought about. One might empirically accept the fact and make the best of it, but I believe one should try to understand, not only in order to make better use of this treatment but because the problem of pain, its physiologic consequences and its treatment, is a highly interesting one. If ophthalmologists can profit by the experiences accumulated during the last twenty years by surgeons in the treatment of pain, I feel they can probably also contribute to this new chapter of physiology and pathology. Most of the present knowledge is due to the work of René Leriche, and his book "The Surgery of Pain" [34] is inspiring.

Leriche and his associates stressed the fact that pain not only has a psychologic effect but can provoke reflexes with important pathologic consequences. Most of these reflexes are vasomotor. In some instances, as I have already mentioned, there is a vasoconstrictor impulse (in obliteration of an artery or vein); in other cases there is a reflex vasodilatation and if this lasts long enough pathologic changes will result. A good example of this process is afforded by a sprained joint. Leriche [35] has taught that when a ligament is torn or distended the afferent painful impulses provoke a strong and lasting vasodilatation, which in turn causes most of the symptoms of sprain. Evidence of this fact is secured by injecting procaine hydrochloride into and around the distended ligament. If this is done early all the usual symptoms of sprain fail to appear—there is no pain, no redness of the skin, no edema and practically no functional impairment. An equivalent situation may occur in the eye, and I need only mention Ricker's [36] views on the consequences of capillary dilatation and increased permeability.

It is possible that physicians are too inclined to consider all symptoms of inflammation as directly caused by an infection, whereas in some instances their immediate cause may be only an abnormal vasodilatation.[37]

At any rate it is worth remembering that pain is not only an unpleasant but an unfavorable condition, that it may be the origin of

34. Leriche (footnote 26 *a* and *b*).

35. Leriche, R., and Fontaine, R.: De la valeur thérapeutique des infiltrations périarticulaires à la novocaïne dans les entorses et les arthritis traumatiques, Presse méd. **40**:280, 1932. Leriche, R., and Policard, A.: Physiologie pathologique chirurgicale, Paris, Masson & Cie, 1930, p. 98. Leriche, R.: Physiologie et pathologie du tissu osseux, ibid., 1939, p. 181.

36. Ricker, G.: Sklerose und Hypertonie der innervierten Arterien, Julius Springer, Berlin, 1927, cited by Duggan, W. F.: Clinical Vascular Physiology of the Retina, read before the New York Society for Clinical Ophthalmology, Nov. 3, 1941. Bailliart, P., in Bailliart, P.; Couleta, C.; Redslob, E., and Velter, E.: Traité d'ophthalmologie, Paris, Masson & Cie, 1939, vol. 5, p. 263.

37. Leriche, R.: Mécanisme de production des hydarthroses et des arthrites traumatiques, Presse méd. **36**:769, 1928.

a vicious circle with pathologic consequences and that the easiest way out is the severance of the afferent pathway.[38]

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DISCUSSION

DR. CONRAD BERENS: His listeners are indeed fortunate to have been informed of Dr. Hartmann's personal experience with some of the newer methods of treating diseases of the eye which are used in France and on the Continent. I have been particularly interested in his references to acetylcholine because I learned of its use from patients who had been treated in France. I, too, have observed no toxic or other deleterious effects from its use, and some of the patients treated seem to have been benefited. I say "seem to have been" because attempts to evaluate any therapeutic measure are fraught with so many pitfalls that I usually find it exceedingly difficult to be sure that a certain treatment used was the deciding factor in the cure.

My results in treating a few patients who had retinitis pigmentosa by the administration of acetylcholine hydrochloride were far from encouraging. In 1 case acetylcholine was injected twice a week for one and a half years, after which I could see no improvement in the patient's fields. However, they were narrowed to within the 5 degree isopter, and she finally lost the vision of one eye in spite of the use of acetylcholine and the performance of bilateral cervical sympathectomy, which produced some distress because of the small pupils.

CASE 1.—Mrs. P. S., aged 50, was seen on July 19, 1939, and a diagnosis was made of retinitis pigmentosa in both eyes. Vision before acetylcholine was administered was, 20/200 in the right eye and 20/20 in the left. One cubic centimeter of acetylcholine hydrochloride solution (0.02 Gm.) was injected twice a week for a year and a half, and on Dec. 2, 1941 the vision was as follows: right, light perception; left 20/25. Other treatment consisted of bilateral sympathectomy, diathermy and vitamin therapy.

There seem to have been some good results from the administration of acetylcholine in cases of thrombosis of the retinal veins, but in most cases attempts also were made to eliminate foci of infection and other vasodilators were used. Therefore, it is difficult to be sure that acetylcholine alone was effective in producing good results. There was remarkable return of vision in a patient who suffered from retrobulbar neuritis and whose vision had been reduced to discerning of hand movements. Nitrites were administered in addition to the acetylcholine, and the sphenoid sinus was opened also. I have seen patients who have had vision restored as a result of this operation alone. It is, therefore, difficult to evaluate the role of acetylcholine in the restoration of vision in this patient.

38. Leriche, R.: A propos du traitement par infiltration novocaïnique de l'épicondylite des joueurs de tennis, des maladies post-traumatiques de même ordre, Presse méd. **44**:99, 1936. Leriche, R.: Leçon d'ouverture du cours de médecine au Collège de France, ibid. **46**:289, 1938.

CASE 2.—Mrs. E. H., aged 45, was seen on July 3, 1941, and a diagnosis was made of retrobulbar neuritis of the right eye. Vision before acetylcholine hydrochloride and sodium nitrite were administered was: right, perception of hand movements; left, 20/20. Sodium nitrite was administered from July 3 to July 21. One injection of acetylcholine hydrochloride was given on July 21. On July 22 sphenoidectomy was performed. Sodium iodide was administered from July 29 to September 26. The vision on Deccember 1 was as follows: right 20/20; left, 20/15.

I agree that the most important single indication for the use of acetylcholine is angiospasm, and I have felt that from the clinical standpoint acetylcholine is as efficacious as some of the newer vasodilators, e. g. erythrol tetranitrate.

Acetylcholine has been administered to several patients who suffered from toxic retrobulbar neuritis due to tobacco and alcohol. In some improvement in visual acuity was noted. However, 2 patients who refused to give up tobacco and alcohol did not regain their normal visual acuity, although they claimed to have taken all the vitamin B necessary and also the vasodilating drugs prescribed. In my experience the most important factor in the treatment of this condition is abstinence from tobacco and alcohol.

I have never prescribed acetylcholine in the treatment of ophthalmic migraine, as I find that most patients suffering from this distress obtain relief from ergotamine tartrate (gynergen) or from a preparation containing phenobarbital with small amounts of ergotamine tartrate and belladonna alkaloid (bellergal).

I believe that the administration of acetylcholine is not worth while in the treatment of advanced arteriosclerosis. Although I prescribed erythrol tetranitrate in the treatment of "choroidosis centralis serosa" after hearing a paper read by W. F. Duggan, I have not been particularly impressed by the results and still rely mainly on attempting to find and eliminate any possible causes of the condition.

Although I have occasionally prescribed acetylcholine and the nitrites in the treatment of optic nerve atrophy, I usually rely on diathermy as being a simpler and possibly equally efficacious treatment.

In the treatment of glaucoma I believe that the circulation of blood within the retina can be maintained by massage as well as by use of acetylcholine and that the circulation of the optic nerve can be maintained more efficaciously by diathermy than by use of acetylcholine.

I have had no experience with retrobulbar injection of procaine hydrochloride in the treatment of thrombosis of the retinal veins, obliterating arteritis or embolism of the central arteries. I believe that the investigations of Leriche, which have been applied to the eye by Dr. Hartmann and Dr. Bailliart, deserve great consideration. I have, however, prescribed atropine sulfate in the treatment of embolism of the central artery and I have also prescribed acetylcholine hydrochloride and other vasodilators, after which usually there was no striking improvement in the condition. Although I have the highest regard for Dr. Hartmann's judgment, I have been a little hesitant in employing retrobulbar injections of procaine hydrochloride or alcohol in cases of uveitis. However, after reading Dr. Hartmann's paper and Leriche's book, I shall try this method of treating painful uveal diseases. Retrobulbar

injections of alcohol in cases of severe pain due to absolute or nearly absolute glaucoma have saved eyeballs which otherwise would have been sacrificed. I was particularly impressed by the results obtained from this method of treatment in a patient who had severe lime burns of the corneas which were not amenable to treatment by transplantation.

With regard to the sphenopalatine ganglion syndrome, I agree with Dr. Hartmann that it is better to apply Bonain solution than to inject the drug into the nerve. In office practice, sometimes I have merely applied a 2 per cent solution of pontocaine hydrochloride to the region of the sphenopalatine ganglion. Dr. Hartmann apparently includes the anterior segment syndrome with the sphenopalatine ganglion syndrome, which has been so well studied by Sluder (Sluder, G.: Concerning Some Headaches and Eye Disorders of Nasal Origin, St. Louis, C. V. Mosby Company, 1920). In the anterior segment syndrome the pain is usually referred to the tip of the shoulder. I have attempted to differentiate these syndromes after reviewing the work of Charlin, which designates the anterior segment syndrome as the syndrome of the nasal nerve (Charlin, C.: Le syndrome du nerf nasal, *Ann. d'ocul.* **168:** 86, 1931). In these cases it seems advisable to apply the anesthetic to the anterior external wall of the nasal fossa on the affected side.

There is no question in my mind that this form of symptomatic treatment is valuable, but I agree with Dr. Hartmann that whenever possible the underlying cause should be sought. I believe that hyperplastic sinusitis is often overlooked as a factor and that bacteria, such as those included in the coliform group, may possibly be causative agents in some cases (Berens, C., and Nilson, E. L.: Experimental Acute Iridocyclitis in Rabbits Produced by Coliform Bacilli Isolated from the Upper Respiratory Tract of Man, *Tr. Am. Ophth. Soc.* **38:** 214, 1940; Ocular Conditions Associated with Coliform Bacteria, ARCH. OPHTH. **26:** 816 [Nov.] 1941). Dr. Hartmann has made an exceedingly important point by suggesting that ophthalmologists could justifiably treat pain as a symptom with benefit to patients. I think ophthalmologists could well establish clinics for the treatment of ocular pain such as that recently established at the New York Hospital for the study and treatment of general pain.

DR. ARNOLD KNAPP: I should like to ask two questions. If I understood correctly, Dr. Hartmann does not like to use acetylcholine in retrobulbar injections. What is his experience in using it subconjunctivally?

Second, the question of alcohol therapy for pain seems to me to be important, as Dr. Berens also has pointed out. I should like to ask Dr. Hartmann what his experience with injections of alcohol has been in cases of painful glaucoma secondary to thrombosis of the central retinal vein.

DR. EDWARD HARTMANN: I must thank the speakers who have just discussed my paper. I did not think that it would cause so much interest.

Dr. Berens is right. I should have mentioned Charlin's syndrome and Sluder's neuralgia, since ocular symptoms are present in both and the treatment is administered intranasally. In the treatment of his nasal nerve syndrome, the Chilean ophthalmologist Carlos Charlin advised that cocaine and epinephrine hydrochloride solution be sprayed into the

anterior part of the nose. This, in fact, is often satisfactory treatment. In the treatment of Sluder's neuralgia it is considered more advisable to anesthetize the sphenopalatine ganglion. Magitot claimed that apart from these two well defined syndromes there are many other lesions of the anterior segment which can be favorably influenced by drugs which act on Meckel's ganglion. Like Dr. Berens, I don't believe that there is much to be expected from these types of treatment when a clot has obstructed a retinal artery. Even if the circulation of blood in the retina is restored it is usually too late for the retinal cells to function again. Improvement can be hoped for only when the patient is seen early, say within an hour after the symptoms have appeared, or when the circulation has not completely stopped. Under such circumstances there may be just enough blood supply remaining to keep the retina alive even if there is not enough for the function to be normal.

In answer to Dr. Knapp's question concerning the retrobulbar injection of acetylcholine, I have injected the drug under the conjunctiva, but this type of injection produces considerable pain and causes a severe reaction. If acetylcholine is to be applied locally, I think it should be injected behind the eyeball, and procaine hydrochloride should be injected just before. Dr. Knapp has also asked me if I have had any experience with retrobulbar injections of alcohol in cases of glaucoma following thrombosis of the retinal veins. The results from this type of treatment are not very good, but there is nothing better to offer, as this type of glaucoma usually is not helped much by administration of pilocarpine or by trephining. If there is pain, however, this can temporarily be relieved by the injection of alcohol. Acetylcholine bears the same name in French as in English. "Acecoline" is the trade name of the acetylcholine prepared by Lematte and Boinot; that is why I have avoided using it.

LIGHT SENSE IN PIGMENTARY DEGENERATION OF RETINA

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In pigmentary degeneration of the retina, the first symptom noticed by the patient is as a rule a disturbance of vision in dim light. This suggests that some form of test of the light sense could be used to detect the incipient stages of the disease, prior to the appearance of changes in the fundus, diminution in the visual acuity or alterations in the visual fields.

A definite diagnosis of pigmentary degeneration in its incipient stages might be of help in determining the efficacy of possible therapeutic measures. Many remedies have been tried, with reports of moderate success by some investigators and of complete failure by others.[1] Hepburn [2] stated the belief that one reason why sympathectomy frequently fails to influence the course of pigmentary degeneration is that it is not undertaken early enough. The same criticism may perhaps be applicable to the negative findings reported for other forms of therapy. In any case it seems reasonable that therapeutic procedures might have a chance of improving or arresting the visual damage if tried at an early stage, before irreversible degenerative changes have taken place.

Tests of the light sense may be of value not only in the early diagnosis of pigmentary degeneration of the retina but in the detection of slight changes in the progress of the condition, to determine whether some particular form of therapy has any effect on the progress of the disease.

REVIEW OF THE LITERATURE

In recent years there has been a renewed interest in clinical studies of the light sense and in particular of the rate of dark adaptation. A review of the literature covering the years 1929 to 1938 was given in a previous article.[3] In this and in a later paper in the series,[4] it was pointed out that in conditions such as pigmentary degeneration of the

Supported by a grant from the John and Mary R. Markle Foundation.

From the Wilmer Ophthalmological Institute of the Johns Hopkins University and Hospital.

1. Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1941, vol. 3, p. 2781.

2. Hepburn, M. L.: Discussion on Retinitis Pigmentosa, Tr. Ophth. Soc. U. Kingdom (pt. 1) **58**:246-255, 1938.

3. Sloan, L. L.: Instruments and Technics for the Clinical Testing of Light Sense: I. Review of the Recent Literature, Arch. Ophth. **21**:913-934 (June) 1939.

(Footnotes continued on next page)

retina, in which the pathologic changes are usually localized in certain retinal areas, tests of the rate of dark adaptation for only one region of the retina may be inadequate. An instrument was described which permits of measurements of the threshold from center to periphery in any desired meridian.

More recently, Mandelbaum [5] reported studies of the light sense in 17 patients with pigmentary degeneration of the retina. His findings lend support to the belief that a measurement of the curve of dark adaptation does not always reveal the earlier stages of visual loss. Mandelbaum used the Hecht-Schlaer adaptometer in these studies. The curve of dark adaptation was determined with a 3 degree test field located 7 degrees temporally to the fixation point. After dark adaptation was complete, measurements were also made of the final threshold at the fixation point, at 20 degrees in the temporal field and at 10, 15 and 20 degrees in the nasal field. Measurements beyond 20 degrees in the horizontal meridian and measurements in other meridians could not be made with this instrument.

The adaptation curves of 3 subjects were shown by Mandelbaum to illustrate early, moderate and advanced stages in the course of the disease. The patient chosen to illustrate an early stage had corrected visual acuity of 20/30 in each eye. Ring scotomas extending from 15 to 30 degrees nasally and from 20 to 50 degrees temporally were found with 2.5 mm. test object at 250 mm. The adaptation curve fell just within normal limits. Tests of the final threshold at other locations, however, showed well defined defects between 10 and 20 degrees in the nasal field and at 20 degrees in the temporal field. Since in this patient perimetric studies showed definite defects, while the curve of dark adaptation was within normal limits, it is obvious that tests of the dark adaptation cannot be relied on to reveal visual loss before there are changes in the visual fields. Determination of the threshold curve from 20 degrees in the nasal field to 20 degrees in the temporal field, however, showed definite evidence of impairment in light sense in some regions of the retina, with normal sensitivity in other regions.

PRESENT INVESTIGATION

The 15 patients [6] studied included the following 4 groups: 1. Four patients illustrating different stages of pigmentary degeneration of the retina in its typical form. 2. Five children in one family for 3 of whom a definite diagnosis of pigmentary degeneration could be made from

4. Sloan, L. L.: Instruments and Technics for the Clinical Testing of Light Sense: III. An Apparatus for Studying Regional Differences in Light Sense, Arch. Ophth. **22**:233-251 (Aug.) 1939.

5. Mandelbaum, J.: Dark Adaptation: Some Physiologic and Clinical Considerations, Arch. Ophth. **26**:203-239 (Aug.) 1941.

6. The patients were referred to me by Dr. Jonas Friedenwald and by Dr. William Rowland.

the ophthalmoscopic and perimetric observations. The father of these children also had pigmentary degeneration. 3. Two patients whose fundi showed pigment deposits of the characteristic bone corpuscle shape, confined almost entirely to the lower peripheral portion of the retina. The visual fields were likewise atypical, and instead of the usual ring scotomas, there were localized defects in the upper fields corresponding to the fundus changes. 4. Four patients with field defects resembling those found in pigmentary degeneration but with little or no evidence of any characteristic pigment deposits.

RESULTS

Cases 1 to 4 have been selected to illustrate the typical threshold gradient curves which are found in different stages of pigmentary degeneration of the retina. Case 1 illustrates a well advanced stage.

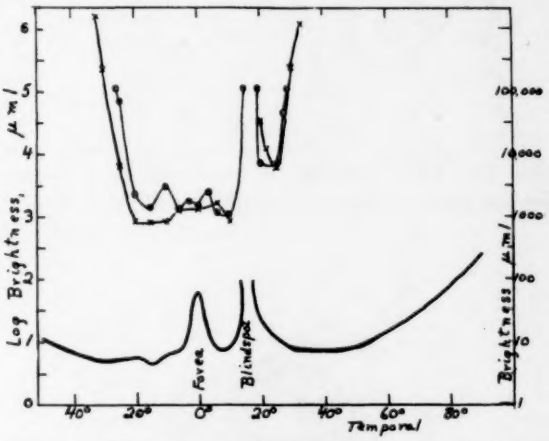

Chart 1 (case 1).—Threshold gradient curves of the right eye in the horizontal meridian. Feb. 1, 1938, -o-o-; May 28, -x-x-; normal curve, — .

CASE 1.—At the time of the first examination, in February 1938, the fundi showed characteristic pigment deposits and there were bilateral incipient cataracts. The corrected visual acuity was 20/30 in each eye. The threshold curve for the horizontal meridian of the right eye and the visual fields for this eye are shown in charts 1 and 2. On reexamination three years later, the corrected acuity was 20/40 — 1. The visual fields were essentially unchanged. The threshold curve for this date also is shown in chart 1. The threshold measurements likewise indicate that there had been no significant progress in the defect in a period of three years. The midregion of the curve, within about 20 degrees from the fixation point, showed the thresholds to be about 2 log units greater than those of the normal eye. At the fixation point itself the threshold was about 1 log unit above normal. There was a rapid increase in the threshold between 20 and 30 degrees in both the nasal and the temporal fields. No measurements could be made in the more peripheral regions because the thresholds

were above the maximum intensity provided by the instrument.[7] In this case a part of the increase of threshold may have been due to the incipient cataract rather than to loss of retinal function.

Case 2.—In this case, as in case 1, both the perimetric studies and the studies of the light sense revealed advanced defects in the peripheral regions. The visual fields of the two eyes were essentially similar. That of the left eye is shown in chart 3. The media were clear; the visual acuity was 20/30 in each eye. The light thresholds at the fixation point and at 6 degrees nasally

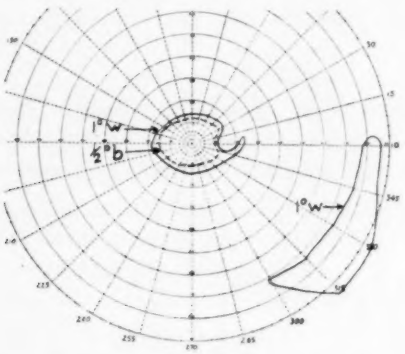

Chart 2 (case 2).—Visual field of the right eye for a 1 degree white and a ½ degree blue test object. The visual acuity was 20/40 — 1.

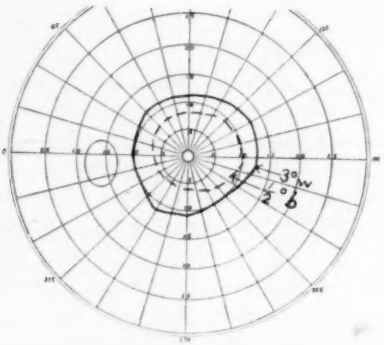

Chart 3 (case 2).—Visual field of the left eye for a 3 degree white and a ½ degree blue test object. The visual acuity was 20/30.

and temporally from the fixation point were within normal limits. The threshold gradient curve rose rapidly in the region between 10 and 20 degrees from the fixation point; beyond 20 degrees the thresholds were above 5 log units.

7. The maximum available intensity in the earlier tests was 5.1 log units. At a later date the instrument was modified so as to provide a maximum intensity of 6.2 log units. Zero on the logarithmic scale corresponds to a brightness of 1 micromillilamberts, 1 log unit to 10 micromillilamberts, etc.

(chart 4). The patient showed characteristic pigment deposits in the periphery of each fundus.

CASE 3.—The defects both in the visual fields and in the light sense were less advanced. The fundi showed typical pigment changes and moderate narrowing of the retinal arteries. There was in the right eye a small punctate centrally located posterior polar cataract. The left eye was selected for study because

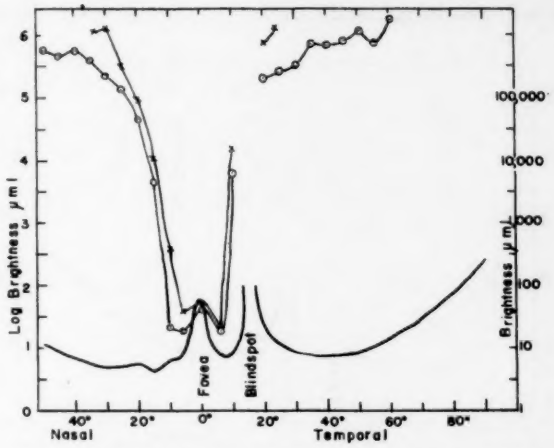

Chart 4 (case 2).—Threshold gradient curves in the horizontal meridian. Right eye, -x-x-; left eye, -o-o-; normal curve, — .

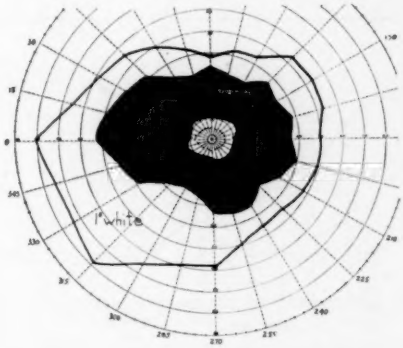

Chart 5 (case 3).—Visual field of the left eye for a 1 degree white and a 1 degree blue test object. The visual acuity was 20/20 —2.

the media were clear. The corrected visual acuity of this eye was 20/20—2. The visual field of the left eye showed a ring scotoma for a 1 degree white object (chart 5). The field for a 1 degree blue object extended about 6 degrees from the fixation point. The threshold curve for the horizontal meridian agreed with the perimetric findings in that the most marked defect was in the mid-periphery (chart 6). In the far periphery of the temporal field the threshold curve was only slightly above the curve for the average normal eye. The

foveal threshold was about 1.5 log units above normal. At 6 degrees from the fovea, the thresholds were about 3.5 log units above normal. In this case, therefore, as in the 2 previous ones, there was relatively less loss of function at the fovea than in the paracentral areas.

CASE 4.—This case illustrates an earlier stage, in which defects in the light sense preceded definite changes in the visual fields. Results for only the right eye will be given. Ophthalmoscopic examination showed in the periphery typical pigment deposits. The visual fields showed no defects when examined with 1

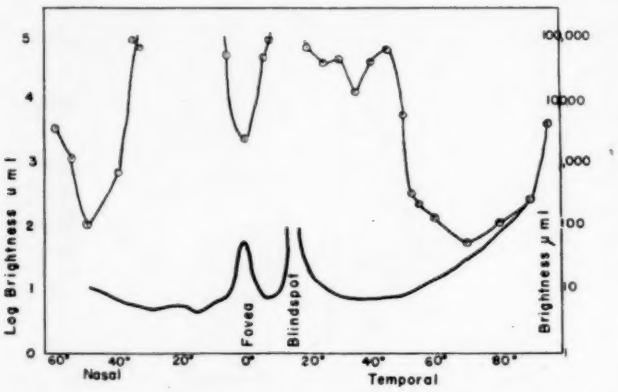

Chart 6 (case 3).—Threshold gradient curve of left eye in the horizontal meridian, -o-o-; normal curve, —.

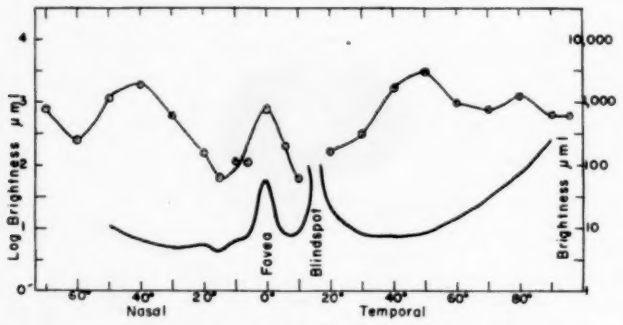

Chart 7 (case 4).—Threshold gradient curve of the right eye in the horizontal meridian, -o-o-; normal curve, —.

degree white, 1 degree blue and 1 degree red test objects. The threshold curve is shown in chart 7. The thresholds were only slightly above normal in the central and in the paracentral regions. The most marked defects occurred at about 40 degrees in the periphery. The results in this case indicate that definite increases in the light threshold of the dark-adapted eye can be found in patients in whom no defects are demonstrable by ordinary perimetric tests. In this particular case, the diagnosis could be made from the ophthalmoscopic observations alone.

In order to determine whether or not the test of the light sense would show characteristic defects prior to the appearance of other clinical signs, I am following a family of 6 children whose father has advanced pigmentary degeneration. At the time the first tests of the light sense were given to these children, 2 of them had typical fundus changes and field defects; a third showed definite defects in light sense at the time of the first test and questionable slight abnormalities in the fields and in

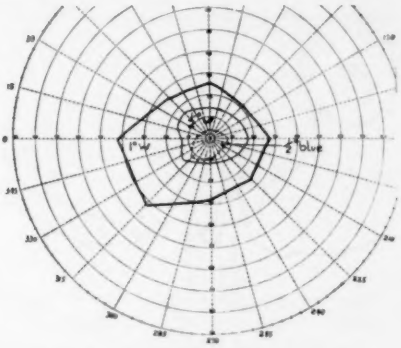

Chart 8 (case 5).—Visual field of the left eye for a 1 degree white, a ½ degree white and a 1 degree blue test object. The visual acuity was 20/15.

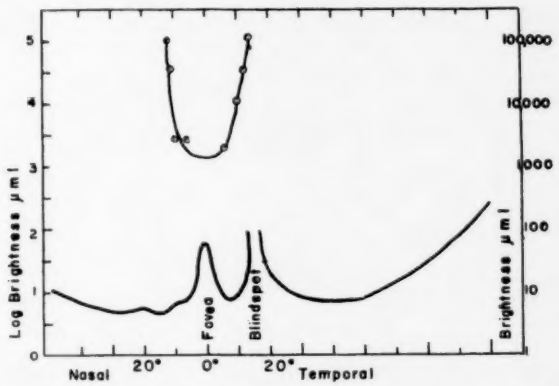

Chart 9 (case 5).—Threshold gradient curve of the right eye in the horizontal meridian, -o-o-; normal curve, —.

the fundi. On reexamination two years later, slight but definite changes in the visual fields and in the fundi were noted, and there was further progression in the light sense defects. The fourth child had at the time of the first examination normal fields and fundi with definitely increased light thresholds. A fifth child is at the time of writing normal by all tests. The youngest child in the family has normal fundi but is as yet too young for studies of the fields or the light sense.

CASE 5.—The oldest child in this family was examined in the Wilmer dispensary in 1929, at the age of 8, and again in 1931. On the first date the fundi were reported to be normal; two years later pepper-like granular dots were noted in the peripheral portions. In 1939 pigmentary changes throughout the entire periphery were seen in both eyes. The visual field and the threshold curve of the left eye for this date are shown in charts 8 and 9. The thresholds at points 15 degrees or more from the fovea were too high to be measured. The threshold data for the central region also showed well advanced defects.

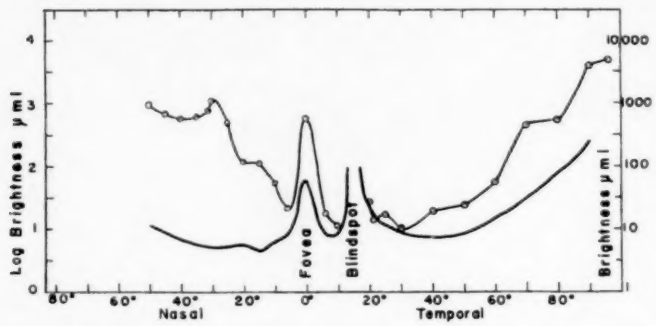

Chart 10 (case 6).—Threshold gradient curve of the right eye in the horizontal meridian, -o-o-; normal curve, —.

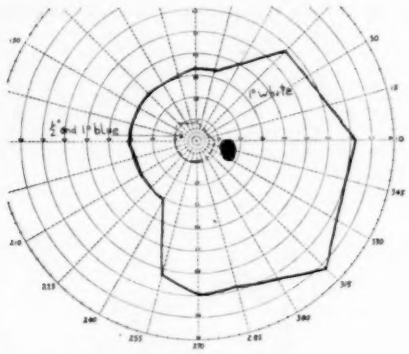

Chart 11 (case 6).—Visual field of the right eye for a 1 degree white, a 1 degree blue and a ½ degree blue test object. The visual acuity was 20/30.

CASE 6.—The second child, examined for the first time in the Wilmer dispensary in 1931, at the age of 8, also showed slight granular pigmentation in the far periphery. On reexamination in 1939 a few pigment spikes and patches of bone corpuscle shape were noted in the right eye and similar but more pronounced pigment patches in the left eye. The threshold curve and the visual field of the right eye were tested at this time and are shown in charts 10 and 11. The visual field for a 1 degree white test object was contracted in the nasal and in the upper field. The field for a 1 degree blue object was definitely reduced in all meridians. The threshold curve for the horizontal meridian showed

definite defects in the nasal portion. The temporal portion was within normal limits except perhaps in the far periphery.

CASE 7.—The third child in this family showed at the age of 14 one or two white spots in the far peripheral portion of the retina of the left eye and a suggestion of fine pepper-like granular dots of pigment in the far peripheral portion of the retina in both eyes. Her corrected visual acuity at this time was normal

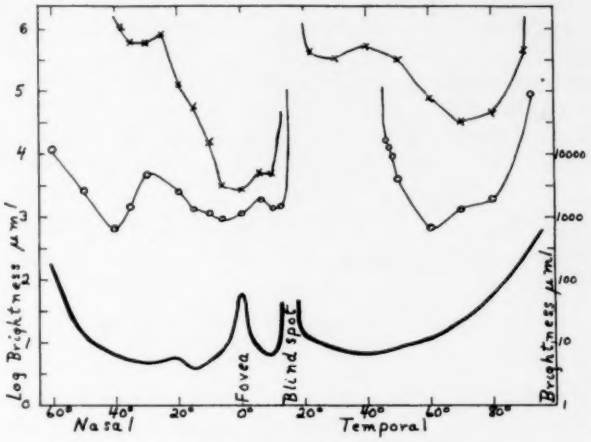

Chart 12 (case 7).—Threshold gradient curves of the left eye in the horizontal meridian. July 13, 1939, -o-o-; June 23, 1941, -x-x-; normal curve, —.

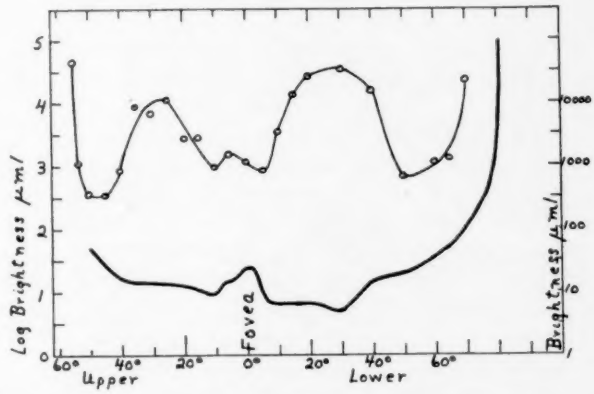

Chart 13 (case 7).—Threshold gradient curves of the left eye in the vertical meridian July 13, 1939, -o-o-; normal curve, —.

in both eyes. The visual fields were also normal, although the limits obtained with a 1 degree blue test object were somewhat variable and there were occasional areas in which the blue test object appeared dim or disappeared momentarily. The test of the light sense at this time showed definite defects. Charts 12 and 13 show the threshold gradient curves for the horizontal and the vertical

meridian of the left eye. The most marked defects occurred in the midperipheral regions between 20 and 40 degrees from the center. Retests two years later showed a further increase in the light thresholds (chart 12). The visual field of the left eye at this time showed a questionable contraction of the limits for a ½ degree white and a slight contraction of the limits for a 1 degree blue test object (chart 14). Ophthalmoscopic examination also showed definite pathologic changes. There were scattered areas of fine granulation in the midperiphery.

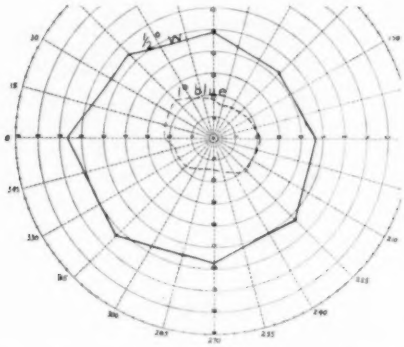

Chart 14 (case 7).—Visual field of the left eye for a ½ degree white and a 1 degree blue test object July 13, 1939. The visual acuity was 20/20 —2.

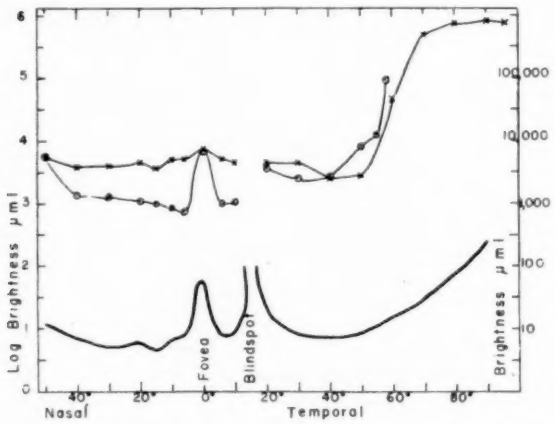

Chart 15 (case 8).—Threshold gradient curves of the right eye in the horizontal meridian. Jan. 30, 1940, -o-o-; Jan. 10, 1942, -x-x-; normal curve, —.

One or two of these areas had small clumps of pigment at the margins. In both eyes there were x-shaped anterior nuclear opacities.

Case 8.—The fourth child was examined for the first time in January 1940, at the age of 13. Ophthalmoscopic examination showed the fundus of the right eye to be entirely normal. Except for a few white spots in the temporal portion of the retina, the left eye was also normal. On reexamination in January 1942, however, some narrowing of the retinal arteries was noted in both eyes and there

were granular pigment dots throughout the periphery in both fundi. Except for a single isolated spot of pigment in the right eye, the pigment deposits did not show the characteristic bone corpuscle shape.

The threshold gradient curve, the visual fields and the corrected visual acuity of the right eye were determined on both dates. Because of the patient's poor comprehension and cooperation, the results of the subjective tests are somewhat unreliable in this case. No defect in the visual fields of the right eye was demonstrable. The corrected visual acuity was 20/30. The light thresholds were about 2 log units above normal except in the far periphery of the temporal field, where the increase in the threshold level was about 4 log units (chart 15). In January 1940 the threshold could not be determined beyond 60 degrees in the temporal field, because at that time the maximum available intensity of the test spot was not great enough. In the other regions of the field, which were tested on both dates, there was evidence of a slight increase in the thresholds during the two year period.

Case 9.—The fifth child was first examined in June 1941 at the age of 9. The visual acuity was 20/15—1 in each eye. Ophthalmoscopic examination showed

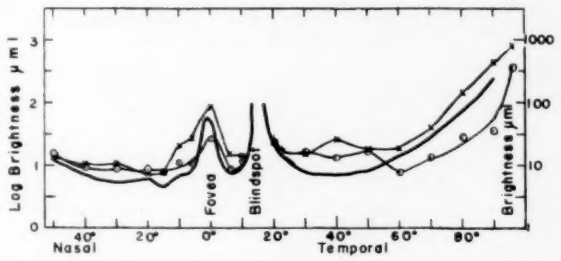

Chart 16 (case 9).—Threshold gradient curves of the left eye in the horizontal meridian. June 25, 1941, -o-o-; December 20, -x-x-; normal curve, —.

mild granular changes and tessellation of the peripheral portions of the fundi. These changes were somewhat more marked in the left than in the right eye. At this time both the visual fields and the threshold curve of the left eye were normal. Reexamination in December 1941 again showed normal visual fields. The fundi showed no essential change. The threshold gradient curve of the left eye, although still within normal limits, showed some increase in the thresholds in the central field and in the far periphery of the temporal field. The results of the tests of the light sense are given in chart 16. The appearance of the fundi and the increase in the light thresholds during a period of six months, in view of the family history, point toward an incipient pigmentary degeneration of the retina.

It should be noted that in the 3 older children in this family, granular pigment dots in the fundi preceded by two years or more the appearance of the typical bone corpuscle–shaped pigment deposits. Two of the 3 younger children now show similar granular pigmentation in the peripheral portions of the fundi. One still has a normal threshold curve;

the other has definitely increased thresholds, which were present at a time when no granular pigmentation was noted.

The next 2 cases illustrate an atypical form of pigmentary degeneration in which the characteristic pigment deposits were well marked in one sector of the peripheral portion of the retina and almost entirely absent in the remaining portion of the retina. Defects in the visual

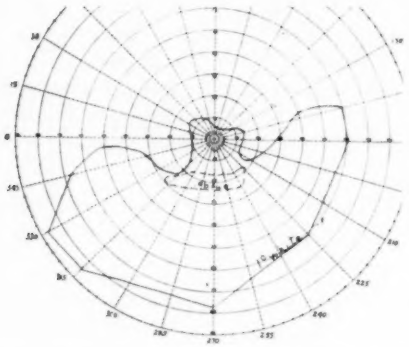

Chart 17 (case 10).—Visual field of the left eye for a 1 degree white and a 1 degree blue test object. The visual acuity was 20/40.

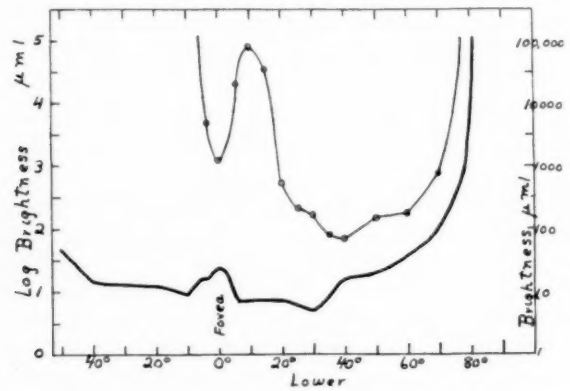

Chart 18 (case 10).—Threshold gradient curve of the left eye in the vertical meridian, -o-o-; normal curve, —.

fields and in the light sense occurred only in the regions where there were pigment deposits.

Case 10.—Each eye showed typical pigmentary deposits and narrowed arteries in only the lower half of the fundus. There were posterior cortical opacities in the right eye; the media of the left eye were clear. The visual fields of the left eye are shown in chart 17. The area blind to a 1 degree white test object included the entire upper field beyond the macular region. The blind area

extended into the lower half of the field also, in the paracentral zone between about 10 and 30 degrees, suggesting an incomplete ring scotoma. A 1 degree blue test object was seen only in a small central area and again in a small patch in the lower field. The threshold gradient was measured in this case in the vertical meridian. The results are shown in chart 18. No measurements could be made in the upper field because the thresholds were above the maximum intensity provided by the instrument. The hump in the curve, centered at about 10 degrees in the lower field, corresponds to the region blind to the 1 degree

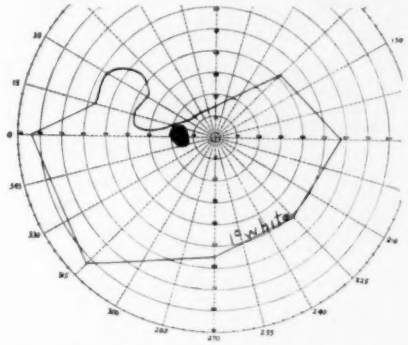

Chart 19 (case 11).—Visual field of the left eye for a 1 degree white test object. The visual acuity was 20/20.

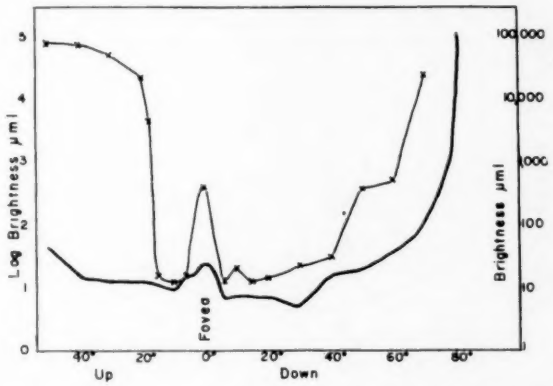

Chart 20 (case 11).—Threshold gradient curve of the left eye in the vertical meridian, -x-x-; normal curve, —.

blue test object. At this point the threshold was about 4 log units above normal. In the far periphery the increase in thresholds was less marked.

Case 11.—The findings in case 11 were similar to those in case 10 although less advanced. The visual fields of the left eye are shown in chart 19. The threshold gradient was measured in both the horizontal and the vertical meridian. The thresholds in the horizontal meridian were within normal limits. The curve for the vertical meridian (chart 20) showed a marked increase in thresholds beyond 15 degrees, which corresponded to the defect in the visual field.

Cases 12 and 13 are examples of so-called retinitis pigmentosa sine pigmento.

CASE 12.—Ophthalmoscopic examination showed well defined narrowing of the retinal vessels. The portion of the retina surrounding the nerve head in both eyes appeared slightly thinned and had a greenish gray cast. Examination with the slit lamp showed granular opacities on the posterior part of the capsule

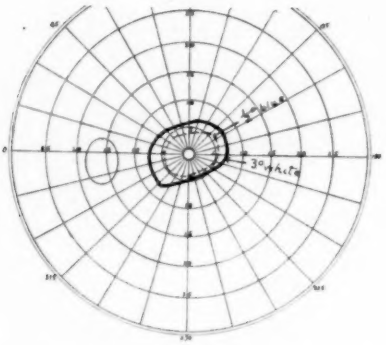

Chart 21 (case 12).—Visual field of the left eye for a 3 degree white and a ½ degree blue test object. The visual acuity was 20/20.

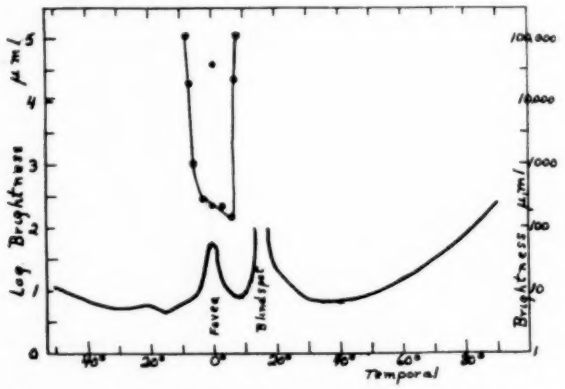

Chart 22 (case 12).—Threshold gradient curve of the left eye in the horizontal meridian, -o-o-; normal curve, —.

of the lens, more marked in the right than in the left eye. The visual fields and the threshold curve of the left eye are shown in charts 21 and 22. A 3 degree white test object was seen only in a small central area extending from 5 to 7 degrees from the fixation point. The field for a ½ degree blue object was 4 to 5 degrees in extent. These results indicate advanced loss of function in the midperiphery and the far periphery. The fact that a ½ degree blue test object was recognized in the macular region shows relatively intact function there. The central visual acuity was normal. The threshold measurements showed

only a slight increase above the average normal level in the foveal region. Beyond 8 degrees, however, the thresholds were too high to be measured. The adaptation curve, tested on the biophotometer, fell within the borderline normal range. This finding is consistent with the relatively normal sensitivity in the central field.

CASE 13.—The findings in case 13 were essentially similar, although the field defects were somewhat less advanced. Ophthalmoscopic examination showed

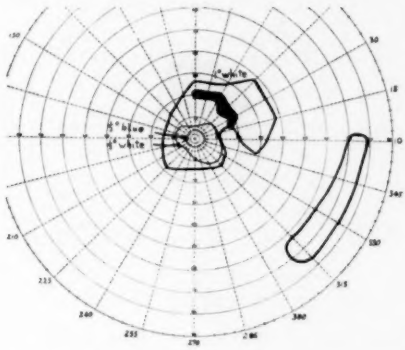

Chart 23 (case 13).—Visual field of the right eye for a 1 degree white, a ½ degree white and a ½ degree blue test object. The visual acuity was 20/30.

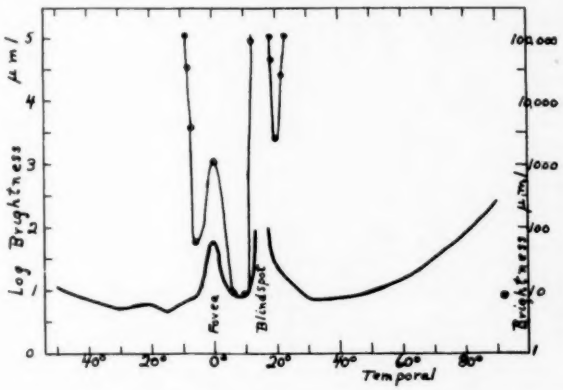

Chart 24 (case 13).—Threshold gradient curve of the right eye in the horizontal meridian, -o-o-; normal curve, —.

in each eye clear media, disks of good color, some narrowing of the retinal blood vessels and a few irregular pigment deposits and small white spots in the temporal periphery. In spite of the negligible fundus changes, there were marked field defects in both eyes. Charts 23 and 24 show the visual fields and threshold curve of the right eye. In the periphery the thresholds were too high to be measured. There was some increase in the foveal threshold. The threshold curve between 6 and 10 degrees, temporal to the fixation point, coincided with

the average normal curve, indicating that in this small zone, at least, the retinal function was still normal. If a curve of dark adaptation had been determined without provisions for control of fixation, according to the technic used in tests with the biophotometer, it would probably have shown no deviation from the normal, because the patient would have directed his eye so that the image of the test field would have fallen on the most sensitive region of the retina. Like-

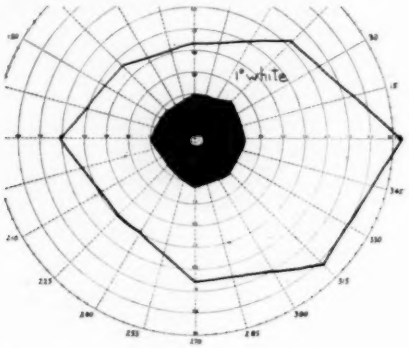

Chart 25 (case 14).—Visual field of the right eye for a 1 degree white test object. The visual acuity was 20/50.

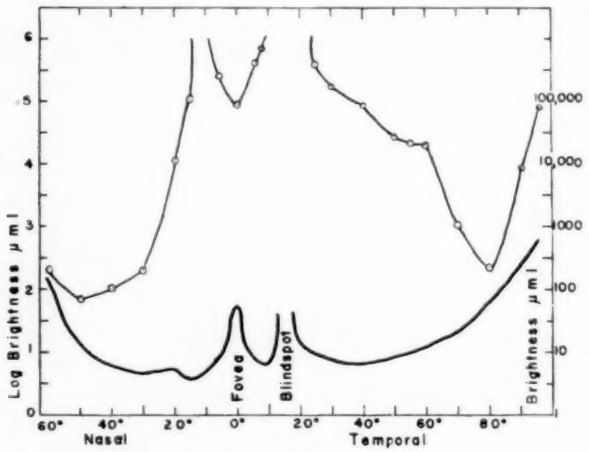

Chart 26 (case 14).—Threshold gradient curve of the right eye in the horizontal meridian, -o-o-; normal curve, —.

wise, if an adaptation curve had been determined at 7 degrees in the temporal field, according to the standard procedure used in making tests with the Hecht adaptometer, the results would probably have shown no abnormality in the rate of dark adaptation.

In cases 14 and 15 there were also well defined field defects similar to those found in typical pigmentary degeneration of the retina, without

any pigment deposits corresponding in location and severity to the field defects.

CASE 14.—Ophthalmoscopic examination showed in both macular regions a few tiny white and yellow spots. There were slight pigmentary changes in the lower part of the left fundus but none in the right. The visual fields of the two eyes were essentially similar and showed absolute ring scotomas. The field for the right eye for a 1 degree white test object is shown in chart 25. The ring

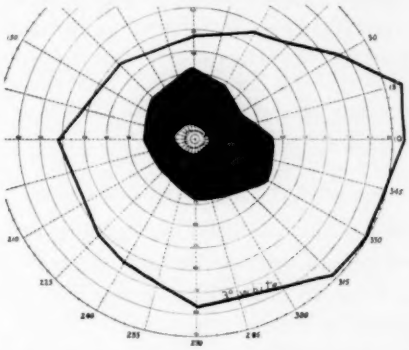

Chart 27 (case 15).—Visual field of the right eye for a 3 degree white and a 1 degree blue test object. The corrected visual acuity was 20/20.

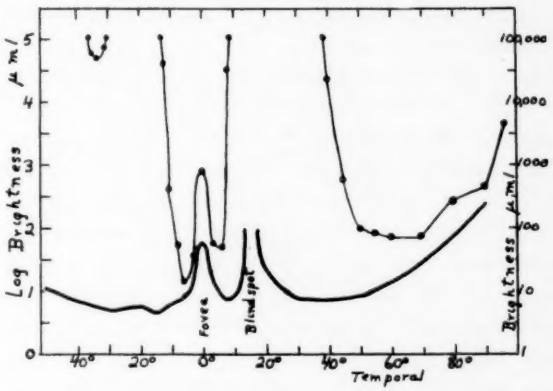

Chart 28 (case 15).—Threshold gradient curve of the right eye in the horizontal meridian, -o-o-; normal curve, —.

scotoma extended to within a few degrees of the fixation point, leaving at the center only a small field 2 to 3 degrees in radius. In this region a 3 degree blue test object was not seen as blue. A 1 degree and ½ degree red test object were recognized as red only at the fixation point. The threshold curve of the right eye is shown in chart 26. The thresholds were far above normal except in the extreme periphery. The thresholds in the macular region, though lower than in the immediately surrounding paracentral areas, were markedly elevated.

The foveal thresholds were more than 3 log units above the average normal values.

CASE 15.—There was marked sclerosis of the retinal vascular system. There were no fundus changes typical of pigmentary degeneration of the retina. The visual fields of each eye showed ring scotomas similar to those found in case 14. The fact that the visual acuity was normal and a 1 degree blue test object was seen in a central area extending about 5 degrees from the fixation point indicates that in this case there was little or no impairment of function in the macular region. The visual fields for the right eye are shown in chart 27 and the threshold curve for this eye in chart 28. As in the previous case, the most marked defects occurred in the midperipheral zone, as would be expected from the perimetric findings. In the far temporal field the thresholds were only slightly above the average normal values. In the nasal periphery, however, the thresholds were too high to be measured except in a small zone between 30 and 35 degrees.

SUMMARY AND CONCLUSIONS

These studies show that defects in scotopic vision occur early in the course of development of pigmentary degeneration of the retina. The defects may consist in a more or less equal increase in the light thresholds throughout the entire visual field. In the majority of cases, however, the threshold gradient curve of the dark-adapted eye shows greater defects in the midperipheral zones than in the far periphery and may show no significant increase in threshold in the central field until the defects in other regions are well advanced. The relatively early involvement of the midperiphery is in accord with the results of ordinary perimetric studies.

The characteristic defects both in the visual fields and in the threshold gradient curve are essentially similar in patients with and without the typical pigmentary deposits in the retina. When pigmentary deposits are present, the location of the most extensive ones corresponds as a rule to the region where the subjective tests show the greatest loss of function.

Since marked functional loss may occur in patients with so-called retinitis pigmentosa sine pigmento and since in typical pigmentary degeneration functional defects may precede ophthalmoscopic evidence of the disease, subjective tests are of importance in diagnosis. The results reported suggest that in the earliest stages defects in scotopic vision may be found to precede visual field defects when the perimetric tests are made under the usual conditions, in which the eye is partially light adapted.

The customary tests of scotopic vision, which measure the rate of dark adaptation of a single region of the retina, cannot be relied on in all cases to reveal the earlier stages of pigmentary degeneration. Although the midperipheral zone usually shows the first and most marked defects, the exact locus of the initial changes varies in different persons, and can be detected only in tests made throughout at least one meridian of the field from center to periphery.

Detection of the incipient stages of functional loss in pigmentary degeneration of the retina by means of tests of scotopic vision may be of importance in determining the fitness of persons for certain occupations which must be carried on in dim illuminations. Such tests may also be of use in the critical evaluation of possible therapeutic measures. Because they are an aid to early diagnosis, they make it possible to test the effect of treatment in the incipient stages of the disease. Quantitative tests of scotopic vision are also of value in determining whether or not there is improvement in visual function as a result of the treatment.

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DETERMINATION OF AXIS AND AMOUNT OF ASTIGMATIC ERROR BY ROTATION OF TRIAL CYLINDER

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HANOVER, N. H.

Dr. Lancaster's statement that only those who know how to use the astigmatic dial can have satisfactory results with it is applicable also to other subjective methods of determining astigmatism. "Practice" alone is not sufficient. Any one desiring to work, for example, with the astigmatic dial or with the cross cylinder not only must be familiar with the optics of the procedure he chooses but must actually "see" the path of the rays, the focal lines and the interval of Sturm as they are being changed by it in the patient's eye. Only those who are really able to visualize such optical phenomena will be able to grasp and, after a few steps, actually foretell the patient's reactions to the measures undertaken in the course of an examination.

In his paper on the use of the cross cylinder, Pascal [1] gave an exemplary demonstration of how such "visualizing" helps in grasping, discussing or teaching problems related to astigmatism. In an example he gave what may be called a "running analysis" of the actual changes in Sturm's interval and in the position of the focal lines during use of the cross cylinder technic for the determination of astigmatism. By means of this running analysis he made clear that fogging into a "mixed condition" is the ideal method of getting the full benefit of the cross cylinder technic in determining the presence or absence and the amount of astigmatism. As Lancaster [2] has taught in the case of the astigmatic dial that only those who know how to fog properly know how to use the astigmatic dial, so in the case of the cross cylinder Pascal has shown that only those who know how to "fog" (to keep the eye in a mixed astigmatic state) for the special purpose of the cross cylinder know how to use it for determining the presence and the amount of the astigmatism.

From the Dartmouth Eye Institute, Dartmouth Medical School.

Read before the New England Ophthalmological Society, Boston, March 17, 1942.

1. Pascal, J. I.: Fundamental Differences Between Crossed Cylinder and Line Chart Astigmatic Tests, Arch. Ophth. **24**:722-730 (Oct.) 1940.

2. Lancaster, W. B.: Subjective Tests for Astigmatism, Especially Astigmatic Charts, Tr. Am. Acad. Ophth., 1915, p. 167.

It may be mentioned in passing that in his recent analysis of the problem Smart [3] arrived at exactly the same result.

As to the question of determining the axis of an astigmatism subjectively, by asking the patient about clearness and blur, Pascal expressed preference for use of the cross cylinder over the method of rotating the trial cylinder in the trial frame, the procedure favored by B. Friedman and also advocated by me.[4] Both Friedman [5] and Pascal [6] gave reasons why they preferred the method they advocated: the rotation of the trial cylinder (Friedman) and the twirling of the cross cylinder (Pascal). Neither, however, based his arguments on actual analysis of examples and of the optical process involved in these procedures.

It seems that the fairest way of evaluating the advantages and the disadvantages of the rotation of the trial cylinder for the determination of the axis of an astigmatism will be to follow Pascal's example. Thus I shall analyze in a few instances what actually happens when one attempts to find the true axis of an astigmatism by this method. I hope that the conclusions arrived at in this manner will be more valid than those referred to, since they will be founded on actual insight into the optics of the procedure.

In order that the question may be treated satisfactorily, the reader must realize that for the purpose of simple mathematical treatment an astigmatic eye can always be conceived as equivalent to an emmetropic eye combined with a certain cylinder at a certain axis. The problems involved in the combination of (*a*) the astigmatic eye with (*b*) the cylinder lens can thus be reduced to problems of a double cylinder (one, which may be called the "eye" cylinder, and another, the "glass" cylinder), and the problem of the proper correction of an astigmatism can be reduced to the problem of finding that "glass" cylinder which neutralizes exactly the "eye" cylinder (i. e. the cylinder thought to be present in the eye). Thus, an eye with a hyperopic astigmatism of 1.00 D. with the rule can be assumed to be equivalent to an emmetropic eye combined with an "eye" cylinder of — 1.00 D., axis 90. Correction of such an eye is accomplished when the "glass" cylinder, + 1.00 D., axis 90, has been found which neutralizes the "eye" cylinder.

Now, assume that by any method the amount of the astigmatism has already been found but not its axis and that a glass cylinder of the

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3. Smart, F. P.: Some Observations on Crossed Cylinders, Arch. Ophth. **24**: 999-1000 (Nov.) 1940.

4. Linksz, A.: Ueber den inversen Astigmatismus und dessen Korrektion, Klin. Monatsbl. f. Augenh. **93**:400, 1934.

5. Friedman, B.: The Jackson Crossed Cylinder: A Critique, Arch. Ophth. **24**:490-499 (Sept.) 1940.

6. Pascal, J. I.: The Jackson Crossed Cylinder, Arch. Ophth. **25**:355-356 (Feb.) 1941.

correct amount has been placed before the eye but with its axis erroneously at 75 degrees. The following two cylinder combination can be assumed in this case to be present before the eye: — 1.00 D. cyl., axis 90 (the eye cylinder) ⊃ + 1.00 D. cyl., axis 75 (the glass cylinder).

Different trigonometric and graphic solutions of such a problem have been given since the time of Donders, Jackson, Prentice and others and can be found in textbooks on geometric optics. I wish to avoid discussing their use, as there are probably many ophthalmologists who wish to use and understand the optics of the procedures mentioned without being able to appreciate their trigonometric presentation, and shall therefore restrict myself to the discussion of the end results of the computations given in the tables and figures accompanying this paper.

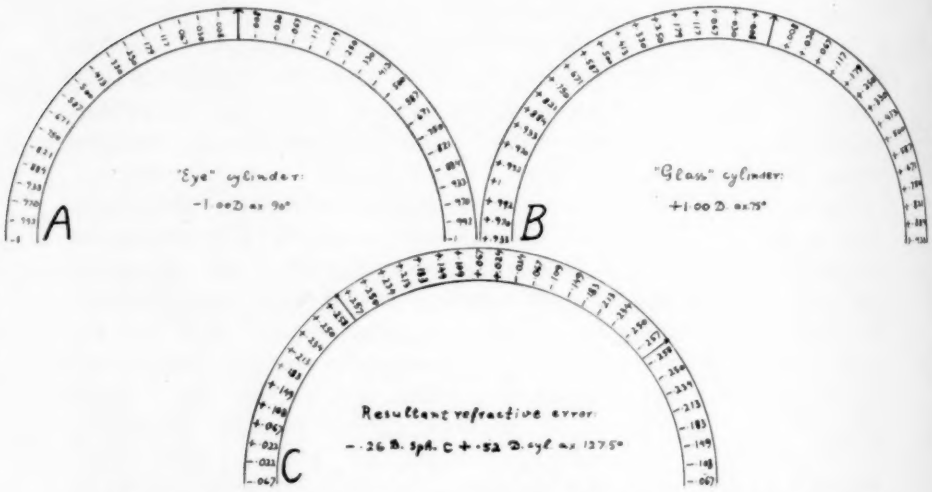

Fig. 1.—*A*, the refractive error in different meridians computed for every 5 degrees in the case of a simple hyperopic astigmatism of 1.00 D., axis 90. The arrow shows the axis of the astigmatism. *B*, the correcting values of a cylinder of + 1.00 D., axis 75 computed for every 5 degrees. The arrow shows the axis of the cylinder. *C*, the resultant refractive error of *A* as corrected by *B* computed for every 5 degrees. The arrows show the maximum minus and the maximum plus meridian, respectively, of this error.

It must be borne in mind that, while the principal meridians of a cylinder designate the two meridians in which the difference of the refractive powers is maximal, there is a steady change in refractive power from one meridian to the other. For example, a cylinder of — 1.00 D., axis 90 has a refractive power of 0.00 D. in the vertical meridian, steadily decreasing to — 1.00 D. as one approaches the horizontal meridian. *A* in figure 1 illustrates the powers in the different meridians of such a

cylinder in steps of 5 degrees.[7] Now, when a plus cylinder of 1.00 D., axis 90, the refractive power of which increases steadily from 0.00 D. in the vertical to + 1.00 D. in the horizontal, is superimposed on this minus cylinder, the sum of the refractive powers of the two cylinders will be 0.00 in every meridian. Thus the two cylinders will have neutralized each other or, in case of an astigmatic eye and a correcting cylinder, the refractive error will be eliminated. However, if the plus cylinder is so superimposed on the minus cylinder that their axes do not coincide, there will be only two meridians in which the sum of the refractive powers of the two cylinders is 0.00 D. Every other meridian will be either

TABLE 1.—*Resultant Refractive Errors When a Simple Hyperopic Astigmatism of 1.00 D., Axis 90 Is Corrected by a Cylinder of the Right Amount While an Error in Axis is Introduced*

Error in Axis, Degrees	Position of Axis, Degrees	Resultant Error
2.5	87.5	−0.04 D. sph. ⌒ +0.09 D. cyl., axis 134
	92.5	−0.04 D. sph. ⌒ +0.09 D. cyl., axis 46
5	85	−0.08 D. sph. ⌒ +0.17 D. cyl., axis 132.5
	95	−0.08 D. sph. ⌒ +0.17 D. cyl., axis 47.5
7.5	82.5	−0.13 D. sph. ⌒ +0.26 D. cyl., axis 131
	97.5	−0.13 D. sph. ⌒ +0.26 D. cyl., axis 49
10	80	−0.17 D. sph. ⌒ +0.35 D. cyl., axis 130
	100	−0.17 D. sph. ⌒ +0.35 D. cyl., axis 50
15	75	−0.26 D. sph. ⌒ +0.52 D. cyl., axis 127.5
	105	−0.26 D. sph. ⌒ +0.52 D. cyl., axis 52.5
20	70	−0.34 D. sph. ⌒ +0.68 D. cyl., axis 125
	110	−0.34 D. sph. ⌒ +0.68 D. cyl., axis 55
30	60	−0.50 D. sph. ⌒ +1.00 D. cyl., axis 120
	120	−0.50 D. sph. ⌒ +1.00 D. cyl., axis 60
45	45	−0.70 D. sph. ⌒ +1.41 D. cyl., axis 112.5
	135	−0.70 D. sph. ⌒ +1.41 D. cyl., axis 67.5

overcorrected or undercorrected, so that a new refractive power will result (or, in the case of an astigmatic eye and a correcting cylinder at the improper axis, a new refractive error).

Thus, in my example of a hyperopic astigmatism of 1.00 D., axis 90 (this, to be sure, means an eye cylinder of *minus* 1.00 D., axis 90) corrected with a cylinder of + 1.00 D., axis 75, an error of — 0.26 D.

7. The formula used for the computation is $D_\alpha = D_o \sin^2 \alpha$, in which D_o is the maximum power of the cylinder, D_α the power in a given meridian and α the angle between the axis and this meridian (Laurance, L.: General and Practical Optics, ed. 3, London, School of Optics, Ltd., 1920, p. 250). That this is not strictly true but rather a convenient approximation has already been pointed out by Pascal (Pascal, J. I.: Power of Cylinders in Oblique Meridians, Arch. Ophth. **22:** 290-291 [Aug.] 1939). Nevertheless, it can be used to advantage for my purposes and makes for an easier understanding of the phenomena I am going to discuss.

sph. ⊃ + 0.52 D. cyl., axis 127.5 (fig. 1) results,[8] causing a blur of letters on the Snellen chart that even a poor observer will recognize. The blur, of course, depends on the amount rather than on the position of the axis of this astigmatism, though its axis is also a factor.

Table 1 gives the resulting errors for a hyperopic astigmatism of 1.00 D., axis 90 when corrected with a cylinder of + 1.00 D., 2.5 to 45 degrees off the true axis.[9] This table (compare figs. 2 *A* and 3) shows that:

1. The resultant astigmatism is always a mixed one, consisting of a myopic error (due to overcorrection) in a certain meridian and a hyperopic error of exactly the same magnitude (due to undercorrection) in the meridian perpendicular to the former.

2. The larger the error in the position of the correcting cylinder, the larger is the amount of the resultant astigmatic error. It is, for example, equal to the amount of the original astigmatism if the error in axis position is 30 degrees and more than half of it if the error is 15 degrees, and even if the error in axis position is no more than 5 degrees the amount of the resultant astigmatism reaches about 17 per cent of the astigmatism to be corrected. In the case of an astigmatism of 3.00 D., this would mean a considerable new astigmatism, of more than 0.50 D., which should produce sufficient blur, especially when compared successively with the visual acuity with the cylinder at the true axis, and may easily be recognized by the patient.

3. The smaller the error in position of the axis of the correcting cylinder, the larger is the difference between the position of the axis of the eye cylinder (i. e. the astigmatism to be corrected) and the axis

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8. It is unfortunate that ophthalmologists are used to this inaccurate way of designating the refractive error by the glass that is necessary to correct it. The resultant refractive error in the case under discussion when designated correctly is + 0.26 D. sph. ⊃ — 0.52 D. cyl., axis 127.5, and a glass of — 0.26 D. sph. ⊃ + 0.52 D. cyl., axis 127.5 is necessary to neutralize, to correct, this error. However, I see no way of avoiding the use of such a familiar method of designation in my presentation. Thus in the following material a refractive error will always be designated by the glass correcting it.

9. The formulas used for the computation of these data are as follows:

$$c = \sqrt{c_1^2 + c_2^2 + c_1 c_2 \cos 2a},$$

$$s = \frac{c_1 + c_2 - c}{2},$$

$$\text{and } \tan 2\beta = \frac{c_2 \sin 2b}{c_1 + c_2 \cos 2b},$$

in which c_1 is the "eye" cylinder, c_2 the correcting cylinder, a the difference in the position of their respective axes in arc degrees, c the resultant cylinder, s the resultant sphere, β the difference between the position of the axis of the eye cylinder and that of the axis of the resultant astigmatic error in arc degrees (Duke-Elder, W. S.: The Practice of Refraction, ed. 3, Philadelphia, P. Blakiston's Son & Co., 1938, p. 257. Suter, W. N.: Handbook of Optics, New York, The Macmillan Company, 1899, p. 148).

of the new, resultant astigmatism. Thus it is just the slight errors in the axis of the correcting cylinder that have the greatest effect on the shifting of the resultant axis, and any further increase in error has only relatively little effect.[10] If the astigmatism is a hyperopic one and the correcting

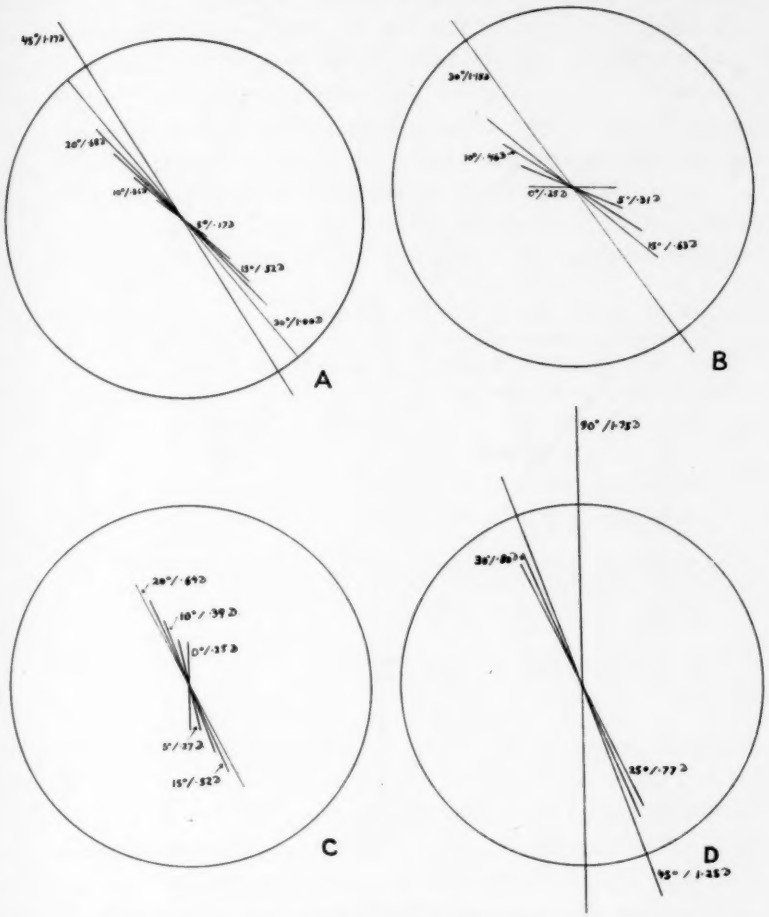

Fig. 2.—Axes and amounts of the resultant astigmatic errors when a hyperopic astigmatism of 1.00 D., axis 90 is (*A*) corrected by a cylinder of proper amount, (*B*) 25 per cent overcorrected and (*C* and *D*) 25 per cent undercorrected.

Of the two numbers given in the form of a fraction adjacent to each of the slanting lines, the first indicates the error in position of the cylinder axis; the second, the amounts of the resultant astigmatism. For example, 5°/17 D. indicates that when the error is 5 degrees the resultant astigmatism is 0.17 D. (or, in general, 17 per cent of the original astigmatism). The slant of the line indicates the axis of the resultant astigmatic error.

10. It will be shown later that this great effect of the small error can be used as the criterion for determining the true axis if the patient looks at the astigmatic dial and not at the letters.

cylinder is a plus cylinder, the axis of the resultant hyperopic astigmatism (the resulting minus meridian) lies to the contralateral side; it is, for example, temporally shifted when the correcting cylinder is placed with

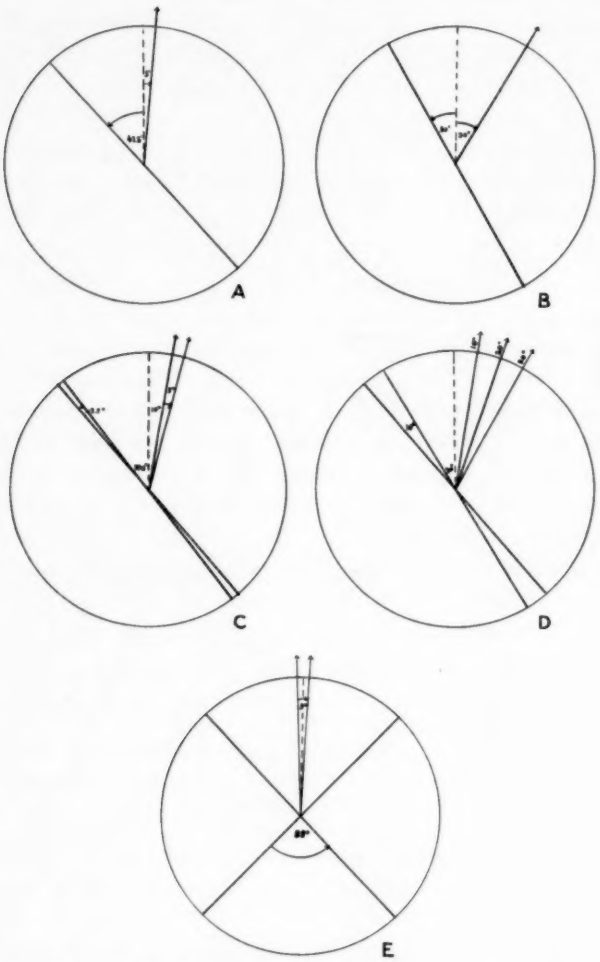

Fig. 3.—Correction by a cylinder of the right amount. *A*, a slight error in axis causes the new axis to "jump" almost 45 degrees in the opposite direction. *B*, the larger the error, the smaller is the difference between the original axis and the resultant axis. *C*, if the starting position is off axis and the cylinder is farther rotated in the wrong direction, the axis of the resultant cylinder will be almost stationary. *D*, an increase of the error in axis causes a slight change in the axis of the resultant cylinder, whereas, *E*, when the cylinder passes the correct axis while it is being rotated, the resultant axis "jumps" almost 90 degrees. (In this figure, as well as in figures 4 and 5, the broken lines indicate the axis of the astigmatism, assumed to be always at 90 degrees; the long radial arrows indicate the positions of the cylinder axis; the slanting diameters indicate the axis of the resultant astigmatism, and the small concentric arrows indicate the direction of the shift.)

its axis nasally from the true axis. A similar analytic treatment would show that the opposite is true with a myopic astigmatism and a minus cylinder.

Table 2 shows the resultant refractive errors in a case in which an attempt has been made to correct a simple hyperopic astigmatism of 4.00 D., axis 90 with a cylinder 25 per cent stronger than necessary, i. e. + 5.00 D., and an error in axis position of 5 to 30 degrees has been introduced. The table (compare figs. 2 *B* and *C* and 4) shows that:

1. The resultant astigmatism, again, is always a mixed one, consisting of a hyperopic error in a certain meridian and a myopic error of a larger magnitude in the meridian perpendicular to the former.

2. The larger the error in position of the axis of the correcting cylinder, the larger, again, is the amount of the resultant astigmatism.

TABLE 2.—*Resultant Refractive Errors When a Simple Hyperopic Astigmatism of 4.00 D., Axis 90, Is Overcorrected 25 Per Cent by a + 5.00 D. Cylinder Placed 5 to 30 Degrees Off the True Axis*

Error in Axis, Degrees	Position of Axis, Degrees	Resultant Error
0	90	−1.00 D. sph. ⊃ +1.00 D. cyl., axis 180
5	85	−1.13 D. sph. ⊃ +1.26 D. cyl., axis 157.5
	95	−1.13 D. sph. ⊂ +1.26 D. cyl., axis 22.5
10	80	−1.42 D. sph. ⊃ +1.84 D. cyl., axis 147.5
	100	−1.42 D. sph. ⊂ +1.84 D. cyl., axis 32.5
15	75	−1.76 D. sph. ⊃ +2.52 D. cyl., axis 140
	105	−1.76 D. sph. ⊂ +2.52 D. cyl., axis 40
30	60	−2.79 D. sph. ⊃ +4.58 D. cyl., axis 125
	120	−2.79 D. sph. ⊂ +4.58 D. cyl., axis 55

It is, for example, about half the amount of the original astigmatism if the error in axis position is 10 degrees and reaches one third of it if the error in the position of the correcting cylinder is not more than 5 degrees.

3. The smaller the error in the position of the axis of the correcting cylinder, the greater, again, is the difference between the position of the axis of the eye cylinder, i. e. of the astigmatism to be corrected, and that of the axis of the resultant astigmatism. Thus, again, the small errors seem to have the greatest effect on the displacement of the resultant axis, the latter, again, always being shifted in the opposite direction if the correcting cylinder is a plus cylinder. In the example in table 2, if the axis is off 5 degrees the axis of the resultant astigmatism is shifted by 67.5 degrees in the opposite direction.[11]

11. This holds true, of course, only if one continues to designate the astigmatism by the same meridian. If a hyperopic astigmatism has been overcorrected, one should continue to designate the resultant astigmatism by a plus cylinder, although it has become a myopic astigmatism. This method of designation is used in the given examples.

At first glance the last-mentioned fact would seem to be of unqualified advantage in determining the true axis. However, this is by no means the case, and one must be cautious to use only slightly stronger cylinders, as Friedman has already advised, in the determination of the true axis.

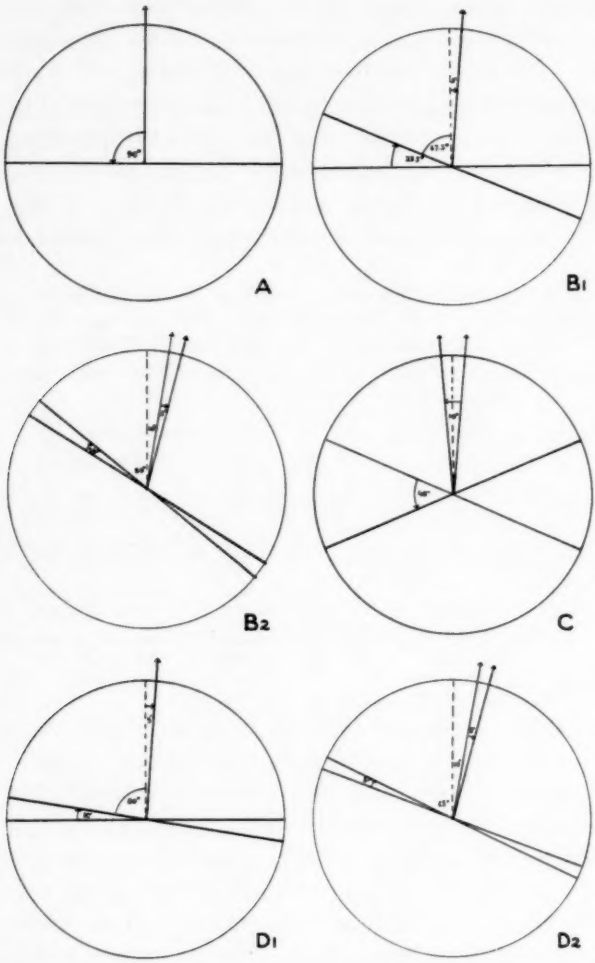

Fig. 4.—Overcorrection. *A*, hyperopic astigmatism, axis 90, overcorrected with a plus cylinder in the proper axis produces an astigmatism with its plus meridian (darkest line of the dial if properly "fogged") in the horizontal. *B*, if the overcorrection is slight, a small error in axis causes a considerable shift of the axis of the resultant astigmatism from the horizontal (B_1), whereas a further increase of the error has a lesser effect (B_2). *C*, if a slightly overcorrected cylinder passes the proper axis while it is being rotated, the jump of the resultant axis is still considerable. *D*, if the overcorrection is considerable, the axis of the resultant cylinder does not shift materially, regardless of whether the error in axis is small (D_1) or large (D_2).

If one overcorrects a hyperopic astigmatism of 1.00 D., axis 90 by 25 per cent with a cylinder of + 1.25 D., axis 90, there has been produced, to start with, a new astigmatism of — 0.25 D. sph. ⊃ + 0.25 D. cyl., axis 180 (compare table 2), i. e. a simple myopic astigmatism against the rule, with its myopic meridian in the horizontal, and the amount of rotation the patient may be able to appreciate subjectively will be relative to the blur caused by this initial astigmatism. If the cylinder axis is rotated to 85, the resultant astigmatism will increase only immaterially (to 0.32 D.), and the myopic meridian (designated in the tables as the axis of the corresponding plus cylinder) will shift from 180 to 157.5 degrees. When the axis of the cylinder is now rotated to 95, the new, resultant myopic meridian will be at 22.5 degrees. This shift is still considerable, though less than when a cylinder of the proper amount was used (compare table 1), and the distortion caused will be enough indication that one has passed the true axis. Furthermore, if one rotates the cylinder axis, for example from 85 to 80 or from 95 to 100, the shift in axis of the resultant cylinder is only 10 degrees (from 157.5 to 147.5 or from 22.5 to 32.5, respectively) as compared with the 22.5 degrees resulting from the rotation of the cylinder from 85 to 90 or from 95 to 90.

Thus, if an astigmatism is overcorrected by 25 per cent, the shift in the axis of the resultant cylinder is still considerably greater in the vicinity of the true axis, to distinguish the latter from the regions farther away. Moreover, the fact that by an error of 5 degrees there has been induced a resultant astigmatism of about 32 per cent, as against 17 per cent when the cylinder is of the correct amount, is of some advantage if the astigmatism is small, as blur and distortion will be more conspicuous and more easily recognized. To rotate a trial cylinder slightly stronger than one thinks correct is therefore recommendable, especially if the astigmatism is not too large.

However, the situation is different when an astigmatism is overcorrected considerably. This may happen easily if the amount of the astigmatism is small (compare table 3 and fig. 2 *D*).

Table 3 [12] shows that if a simple hyperopic astigmatism of 1.00 D., axis 90 is overcorrected by 100 per cent with a + 2.00 D. cylinder in the true axis, a new (simple myopic) astigmatic error of 1.00 D. with its plus (myopic) meridian at 180 degrees results. If the axis of the cor-

12. The examples in tables 2 and 3 have been chosen purposely. The absolute amounts of the resultant refractive errors caused by overcorrection are the same in the two—as long as the overcorrecting cylinder is in the true axis—namely, — 1.00 D. sph. ⊃ + 1.00 D. cyl., axis 180 or — 1.00 D. cyl., axis 90, although in the first example the overcorrection is 25 per cent and in the second it is 100 per cent. However, as soon as the overcorrecting cylinder is not in the true axis the behavior of the resultant astigmatism in the 2 cases is quite different. The reader can readily verify this by comparing tables 2 and 3.

recting cylinder is rotated to 85 the resultant astigmatism scarcely increases and the meridian shifts only to 170 degrees. If one rotates it to 95, the meridian shifts to 10 degrees. The actual rotation of the axis must be as much as 15 degrees off the true axis in either direction in order to cause a shift in the resultant cylinder axis of 25 degrees, while the amount of the resultant astigmatism increases only by 24 per cent. But rotations of such an amount are of dubious value. Pascal[6] cited as the greatest advantage of the cross cylinder technic in determining the true axis the suddenness of the occurring change. This advantage is certainly lost if the trial cylinder must be rotated from 75 to 105 degrees in order to get a shift of 50 degrees in the resultant axis and a change in astigmatism of about 25 per cent. It is thus only with

TABLE 3.—*Resultant Refractive Errors When a Simple Hyperopic Astigmatism of 1.00 D., Axis 90, Is Overcorrected 100 Per cent by a + 2.00 D. Cylinder Placed 5 to 30 Degrees Off the Proper Axis*

Error in Axis, Degrees	Position of Axis, Degrees	Resultant Error
0	90	−1.00 D. sph. ⊂ +1.00 D. cyl., axis 180
5	85	−1.01 D. sph. ⊂ +1.02 D. cyl., axis 170
	95	−1.01 D. sph. ⊂ +1.02 D. cyl., axis 10
10	80	−1.06 D. sph. ⊂ +1.12 D. cyl., axis 160
	100	−1.06 D. sph. ⊂ +1.12 D. cyl., axis 20
15	75	−1.12 D. sph. ⊂ +1.24 D. cyl., axis 155
	105	−1.12 D. sph. ⊂ +1.24 D. cyl., axis 25
30	60	−1.37 D. sph. ⊂ +1.65 D. cyl., axis 135
	12	+1.37 D. sph. ⊂ +1.65 D. cyl., axis 45

discrimination that a stronger cylinder than the correct one should be used for the rotation test.

One now has to investigate the resultant astigmatism in the case in which weaker than correct cylinders are rotated in the trial frame. While the amounts of the resultant astigmatism, due to the uncorrected residue of the original astigmatic error, are naturally greater than when a cylinder of the correct amount is being rotated, the shift in the axis is not sufficient to make the use of a cylinder weaker than the correct one advisable.

Table 4 shows the interesting behavior of the axis of the resultant astigmatism when a hyperopic astigmatism, axis 90, is corrected by a plus cylinder 25 per cent weaker than necessary. It will be seen (compare figs. 2 *C* and *D* and 5) that:

1. The resultant astigmatism, again, is always a mixed one, consisting of a myopic error in a certain meridian and a hyperopic astigmatism of a larger magnitude in the meridian perpendicular to the former.

2. The larger the error in the position of the axis of the correcting cylinder, the larger, again, is the amount of the resultant astigmatic

error; however, there is almost no increase in the critical position, i. e. when the cylinder is rotated a few degrees in either direction from the proper axis, while, at the same time, there is little change in the axis of the resultant cylinder.

3. In contradistinction to the behavior of the axis of the resultant cylinder in the examples given in tables 1, 2 and 3, the smaller the error in the position of the axis of the correcting cylinder, the smaller is, at first, the difference between the position of the axis of the astigmatic error to be corrected and that of the axis of the resultant astigmatism. With an increasing error in axis position, the displacement of the resul-

TABLE 4.—*Resultant Refractive Errors When a Simple Hyperopic Astigmatism of 1.00 D., Axis 90, Is Undercorrected 25 Per Cent by a + 0.75 D. Cylinder and An Error in Axis Is Introduced*

Error in Axis, Degrees	Position of Axis, Degrees	Resultant Error
0	90	0.00 D. sph. ⊃ +0.25 D. cyl., axis 90
5	85	−0.02 D. sph. ⊃ +0.27 D. cyl., axis 102.5
	95	−0.02 D. sph. ⊂ +0.27 D. cyl., axis 77.5
10	80	−0.07 D. sph. ⊃ +0.39 D. cyl., axis 110
	100	−0.07 D. sph. ⊂ +0.39 D. cyl., axis 70
15	75	−0.13 D. sph. ⊃ +0.52 D. cyl., axis 112.5
	105	−0.13 D. sph. ⊂ +0.52 D. cyl., axis 67.5
20	70	−0.20 D. sph. ⊃ +0.64 D. cyl., axis 115
	110	−0.20 D. sph. ⊂ +0.64 D. cyl., axis 65
25	65	−0.26 D. sph. ⊃ +0.77 D. cyl., axis 115
	115	−0.26 D. sph. ⊂ +0.77 D. cyl., axis 65
30	60	−0.32 D. sph. ⊃ +0.80 D. cyl., axis 112.5
	120	−0.33 D. sph. ⊂ +0.80 D. cyl., axis 67.5
45	45	−0.50 D. sph. ⊃ +1.25 D. cyl., axis 110
	135	−0.50 D. sph. ⊂ +1.25 D. cyl., axis 70
90	180	−0.75 D. sph. ⊃ +1.75 D. cyl., axis 90

tant axis first increases until it reaches a certain maximum inclination and then diminishes, while the error in the position of the correcting cylinder is increased further.

Further examples would show that the more nearly the power of the "too weak" cylinder approaches the right amount, the larger is the maximum inclination of the axis of the resultant cylinder, with 45 degrees in either direction as its limit when the cylinder is correct. Conversely, the greater the error in the power, i. e. the weaker relatively a cylinder is, the smaller is the difference between the original axis and the maximum inclination.

Thus, in summary, it may be stated that only if a cylinder of approximately the correct amount is used (its approximate value, of course, must already have been determined by some method), can one expect

that rotation of this cylinder in either direction in the vicinity of the true axis will cause considerable displacements of the axis of the resultant astigmatism. A "slightly" stronger cylinder may have the advantage of increasing the amount of the resultant astigmatism, thus rendering

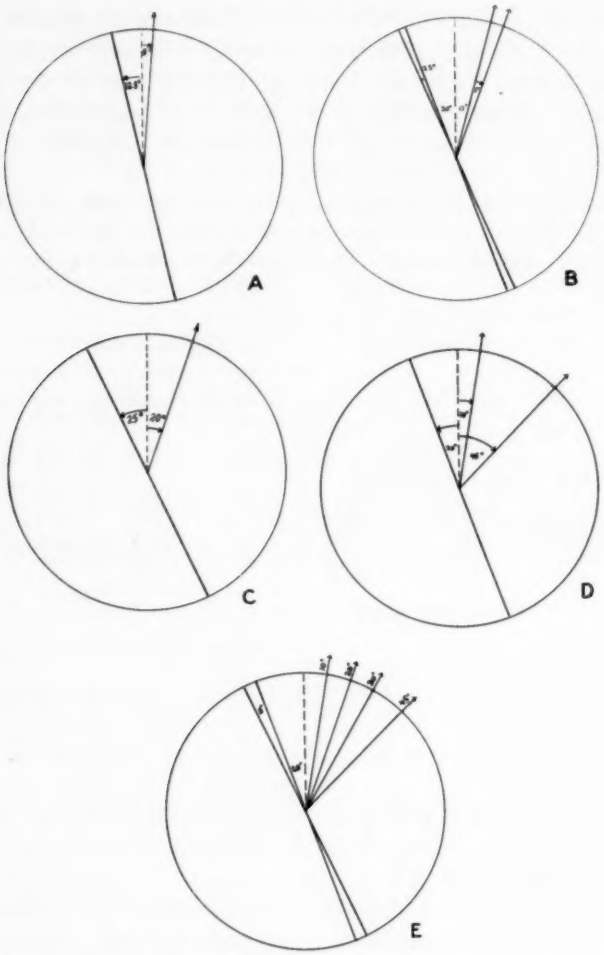

Fig. 5.—Undercorrection. *A*, a slight error in axis causes the axis of the resultant astigmatic error (the blackest line of the dial when properly "fogged") to incline slightly to the opposite side. *B*, when the error in axis increases, this inclination increases slightly. *C*, the inclination reaches a maximum by a certain amount of rotation of the cylinder and decreases with further rotation. *D*, there are two different errors in axis for which the inclination is equal. *E*, the axis of the resultant astigmatism is almost stationary and in the vicinity of the expected axis while the cylinder is turned 20 or more degrees, indicating that the cylinder is too weak.

its subjective detection easier while causing not too considerable a decrease in the amount of the "shift." Rotation of a weaker cylinder is disadvantageous altogether.

In 1934, when I first advocated this technic, I had the patient look at the lowest line of a distance test chart he was able to read. The same method is advocated by Friedman. However, I have since changed my technic, as with a small amount of astigmatism the method still had quite a margin of error. If a patient has a considerable astigmatism, he is usually able to detect an error of 2.5 degrees (or less) with the Snellen chart; for example, a correcting cylinder of 4.00 D. would cause a resultant astigmatism of about 0.36 D. when rotated 2.5 degrees out of the proper position, causing blur and distortion of the small letters. However, with an astigmatism of 1.00 D., the correcting cylinder has to be turned 7.5 degrees (compare table 1) in either direction in order to produce a resultant astigmatism of about 0.25 D., which does not cause enough blur to be recognized by poor observers, especially as it is a partially myopic astigmatism. On the other hand, while overcorrection does cause a more considerable astigmatism, the differences in the resultant amounts and axes are not always sufficient to be evaluated for the subjective discrimination of the true axis with the Snellen chart (tables 2 and 3).

I have therefore refined my technic and combined it with the use of the astigmatic dial. My results are especially satisfactory, since I use the astigmatic chart of Lancaster [2] and Regan,[13] which has a line for every 10 degrees, the lines being so computed that they are readily recognized with slight fogging. With this chart it is possible to detect an astigmatism of 0.12 D. in a patient having a good faculty of observation, while the patient actually "sees" the axis of the resultant cylinder. Thus it becomes superfluous to rely on rather hazy distinctions of "distortion" and "blur" of letters and successive comparisons of distortions and blurs of different degree.

Of course my method, as does the cross cylinder technic, serves merely the purpose of ultimate refinement of the refractive correction, and the amount of the spherical and the astigmatic error must first be determined as accurately as possible by any method preferred, so that the patient will have almost the maximum visual acuity which is to be expected.

If this purpose has already been accomplished, the next step is fogging according to the amount of hyperopia one expects to be produced by rotating the cylinder out of the axis which was found to be nearly

13. Regan, J. J.: Astigmatic Dials in Refined Refraction, Arch. Ophth. **17**:788-796 (May) 1937.

correct.[14] For example, in the case of an astigmatism of about 1.00 D., fogging by a + .25 D. sphere is sufficient. This does not mean, however, that in the case of an astigmatism of 4.00 D. it is necessary to fog four times as much, since the amount of rotation necessary to produce a sufficient astigmatic error will be much smaller than in the case of an astigmatism of 1.00 D.; thus the resultant errors produced will not be four times as great.

When the preliminary examinations lead to a correct cylinder in the correct axis, all the lines on the dial will appear equal to the patient. If the patient is already familiar with the chart, his statement will be reliable. Otherwise it may not be, because in the beginning the patient does not recognize what he is supposed to look for. Rotation of the cylinder to such a degree as would produce an astigmatism of at least 0.50 D. (this means, of course, less rotation in the case of a higher astigmatism) will then make the lines definitely unequal, with the "blackest" line of the chart slanting in the direction opposite to that of the plus cylinder or in the same direction as the minus cylinder which has just been rotated (fig. 3*A*).

The most startling point of the procedure for both the patient and the examiner, however, is that while the cylinder is rotated on one side of the true axis, the change of the "blackest" line or lines will be inconsiderable (as figure 2 and table 1 indicate; for example, rotating the cylinder as much as from 80 to 75 in case of an astigmatism at 90 degrees will shift the axis of the resultant cylinder only from 130 to 127.5 degrees), but as soon as the 90 degree line has been passed, the indicated axis will suddenly jump over into the region of 45 degrees (fig. 3*E*). This, according to my experience, is one of the most accurate indications of the true axis of an astigmatism. And it certainly has the advantage of the cross cylinder technic that was so emphatically pointed out by Pascal, namely the suddenness of the change.

To repeat: If, for example, a hyperopic astigmatism in a nearly vertical axis is expected and a plus cylinder of the proper amount is being rotated from, say, 85 to 80, or from 90 to 95, and there is no sudden change in the indicated slanting axis of the resultant cylinder, the correct axis has not been passed. On the other hand, if, while the cylinder is being rotated from, say, 85 to 90 the "blackest" line of the dial "jumps" over from about 135 to about 45 degrees, the true axis is in between these two points. Naturally, the stronger the rotated cylinder, the smaller will be the rotations necessary to elicit this phenomenon. If one does the test—as shown by the examples in this

14. It would not be in line with the purpose of this paper to enter into the question of how to fog properly. This has been done in the quoted papers by Lancaster[2] and Regan,[13] which should be read by every one who wants to know how to use the astigmatic dial. It should merely be emphasized again that without proper fogging the astigmatic dial cannot be used successfully.

paper—with a plus cylinder, the "blackest" line will always "jump" away from the direction in which the axis of the cylinder has been rotated. If a minus cylinder is used, the blackest line "jumps" toward the axis of the cylinder.

Moreover, this phenomenon can also be used for refining the determination of the amount of astigmatism. If, for instance, the axis of a hyperopic astigmatism is expected to be around 90, and by rotating the axis of the correcting cylinder in the vicinity of 90 the "blackest" line appears to move near the horizontal (of course only if the fogging is proper), the correcting cylinder is definitely too strong (tables 2 and 3 and fig. 4); if it shifts back and forth nearer to the vertical, the correcting cylinder is definitely too weak (table 4 and fig. 5); if it shifts about 45 degrees off axis, the cylinder is most probably correct. When a fairly strong astigmatism is corrected with a cylinder that is too weak, even the phenomenon of maximum inclination and backward swing of the "blackest" line can be experienced.

Only the use of the Lancaster-Regan dial reveals all the possibilities of rotation of the trial cylinder in determination of the true axis of an astigmatism. It raises this subjective test from a more or less accurate guessing at the blurring and distortion of letters to an exact test, competing in accuracy with the most precise retinoscopic examination.

It will be appropriate to close this paper with a similar but short analysis of the use of the cross cylinder in determining the true axis. The cross cylinder —0.50 D. ⊃ + 0.50 D., which is taken as an example, is obviously identical with the lens—0.50 D. sph. ⊃ + 1.00 D. cyl. Its powers in the different meridians computed for every 5 degrees are given in figure 6.

There is no need to show how in the case of an astigmatism of known axis the cross cylinder can be used to determine the amount of the astigmatism, as this has been done repeatedly. Obviously, for this purpose one has to apply the cross cylinder with its principal meridians superimposed on the principal meridians of the astigmatism to be corrected. In the case of a simple hyperopic astigmatism of 1.00 D., axis 90 (I now disregard the question of accommodation and fogging), the cross cylinder with the white dots in the vertical (indicating the axis of the plus cylinder) produces a myopia of 0.50 D., while twirling the cross cylinder produces a new refractive error of — .50 D. sph. ⊃ + 1.50 D. cyl., axis 90. The patient obviously chooses the first setting.

To determine the true axis of an astigmatism with the cross cylinder, one has to use it with its principal meridians 45 degrees off the expected axis.

Figure 7 shows that when there is a hyperopic astigmatism of 1.00 D., axis 90, and the cross cylinder is placed with the axis of the plus component at 45 degrees, a new, resultant astigmatism of — 0.20 D. sph. ⊃ + 1.40 D. cyl., axis 112.5 is produced. Now if the cross cylinder is

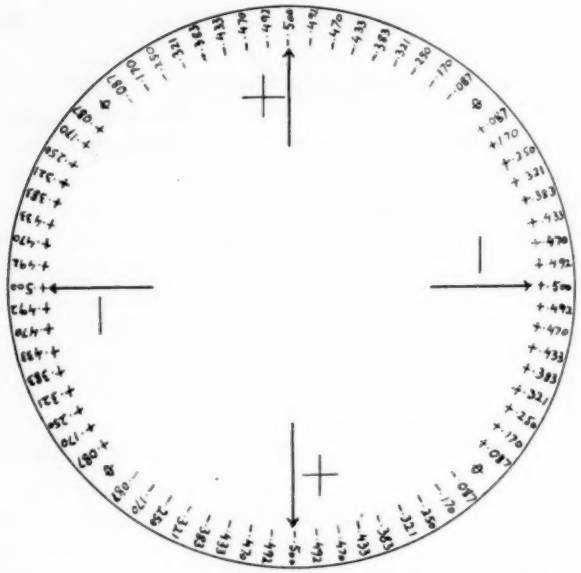

Fig. 6.—The refractive powers of the cross cylinder $-0.50 \bigcirc + 0.50$ computed for every 5 degrees.

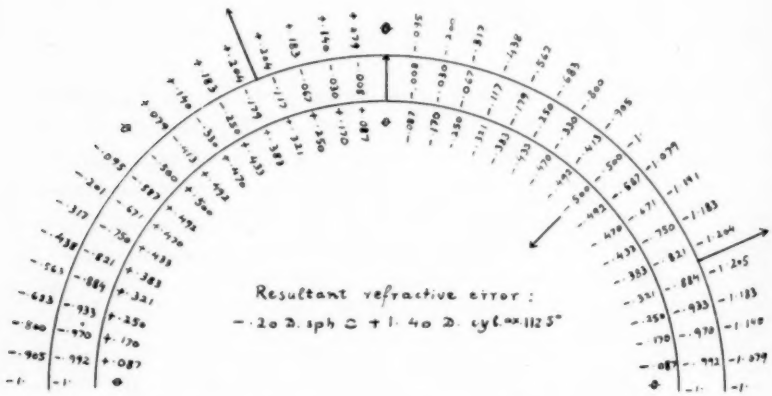

Fig. 7.—The resultant refractive errors computed for every 5 degrees when a hyperopic astigmatism of 1.00 D., axis 90 is tested with the cross cylinder — 0.50 D. $\bigcirc$ + 0.50 D., with the axis of its plus component at 45 degrees. Center circle: refractive errors computed for every 5 degrees, the arrow showing the axis of astigmatism. Inner circle: refractive powers computed for every 5 degrees of the cross cylinder, the arrow showing the plus axis. Outer circle: resultant refractive errors computed for every 5 degrees. The arrows show the maximum minus and the maximum plus meridian, respectively, of the resultant refractive error.

twirled, an astigmatism of the same amount results with axis 67.5. Thus blur and distortion are the same, and this fact is appreciated as indicating that the true axis, 90, of the astigmatic error has been found.

If with the axis of the astigmatism at, say, 105 one erroneously assumes it to be at 90 and twirls the cross cylinder in the position mentioned (45 to 135 degrees), the resultant astigmatism will be — 0.36 D. sph. ⊃ + 1.72 D. cyl., axis 120 in the first position and + 1.00 D. cyl., axis 75 in the second position and the blur, of course, considerably less in the latter position. Thus one will immediately see that the assumed axis is incorrect and that the proper axis is closer to the second position.

However, the cross cylinder is not used only in the way just described, i. e., without a correcting cylinder before the eye, in which case its optics is simple; Smart,[15] Crisp,[16] Pascal [1] and many other authors have suggested using it with the tentative correcting cylinder already in position. It is clear from what has been elaborated in this paper that when an astigmatism in a certain assumed axis is corrected by a cylinder, a new astigmatism in an altogether different axis is produced if the assumed axis is not the true axis. It is this new resultant, or secondary, astigmatism with an axis different from the axis of the original astigmatism which is being subjected to the twirling of the cross cylinder, and it is the blur and distortion caused by it which is being compared with the blur and distortion of a new, tertiary astigmatism.

Fortunately this fact does not interfere with the usefulness of the test, as can be seen from the following example:

If one assumes that the patient has a hyperopic astigmatism of 1.00 D., axis 75 and puts a + 1.00 D. cyl., axis 75 in front of his eyes, whereas the true axis is at 90, a new astigmatism of — 0.26 D., sph. ⊃ + 0.52 D. cyl., axis 127.5 results (table 1). Since one assumes, however, that the astigmatism is at 75 degrees, the cross cylinder is twirled in the position of 30 to 120 degrees. A new, tertiary astigmatism of — 0.75 D. sph. ⊃ + 1.50 D. cyl., axis 122.5 will be produced in the first position and of 0.26 D. sph. ⊃ + 0.52 D. cyl., axis 22.5 in the second position. The patient will readily recognize such a difference and call the second position better, thus inducing the refractionist to shift the axis of the cylinder toward 120 degrees.

One will presently see how striking the differences are and will not be surprised that the cross cylinder technic is used so extensively and is recognized as one of the best methods of finding the true axis of an astigmatism.

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15. Smart, F. P.: Crossed Cylinders in Refraction, Virginia M. Monthly **57:** 506-509 (Nov.) 1930.

16. Crisp, W. H.: The Cross-Cylinder Tests Especially in Relation to the Astigmatic Axis, Tr. Ophth. Soc. U. Kingdom **51**:495-514, 1931.

Moreover, the test is just as effective if the cross cylinder is twirled in the 45 to 135 degree position regardless of the assumed position of the axis of the astigmatism to be corrected. The case in table 2, in which a hyperopic astigmatism of 4.00 D., axis 90 is present and one of 5.00 D., axis 85 is assumed, may serve as an example. The correcting cylinder produces a resultant astigmatism of — 1.13 D. sph. ⊃ + 1.26 D. cyl., axis 157.5. When the cross cylinder is twirled in the position of 45 to 135 degrees, the astigmatic error in the first position increases to — 1.54 D. sph. ⊃ + 2.11 D. cyl., axis 157.5, whereas in the second position it decreases to — 0.03 D. sph. ⊃ — 0.97 D. cyl., axis 95, an improvement immediately recognized by the patient, inducing a shift of the correcting cylinder toward 135 degrees. Of course, as is rightly emphasized by Friedman, rotating the trial cylinder 5 degrees in either direction produces almost as striking differences, as the resultant astigmatism decreases to — 1.00 D. sph. ⊃ + 1.00 D. cyl., axis 180 when the cylinder is being rotated 5 degrees counterclockwise and increases to — 1.42 D. sph. ⊃ + 1.84 D. cyl., axis 147.5 when it is rotated 5 degrees clockwise (table 2).

It thus seems that the two methods can be used to equally great advantage by those who know how to evaluate them, so long as the blur and the distortion of the Snellen chart are used as the criterion for finding the axis, the cross cylinder probably giving the more striking differences. The advantage of rotation of the trial cylinder becomes obvious only when it is used in connection with the Lancaster-Regan dial, as has been shown previously in this paper, thus inducing the patient to make an actual observation of the changing axis of resultant astigmatic errors instead of relying on his successive comparisons of blur and distortion.

SUMMARY

When an astigmatism is corrected by a cylinder at the wrong axis, a new astigmatic error results, the power and the axis of which depend on (1) the error in axis position and (2) the relative power of the correcting cylinder.

The larger the error in axis position, the larger is the resultant astigmatism, regardless of whether or not the correcting cylinder is right, while the axis of the resultant astigmatism shows a different and characteristic behavior contingent on whether the correcting cylinder is (*a*) right, (*b*) too strong or (*c*) too weak.

When the correcting cylinder is right the smallest rotation of the cylinder to one side throws the axis of the resultant astigmatism almost 45 degrees in the opposite direction, while a further increase of the error in axis position has almost no effect on the resultant axis.

When the correcting cylinder is too strong but is in the true axis, a new astigmatism with its axis 90 degrees to the axis of the original

astigmatism is produced. The greater the relative overcorrection, the less will be the change in the axis of the resultant astigmatism when the axis of the correcting cylinder is rotated.

When the correcting cylinder is too weak and is in the true axis, part of the original astigmatism remains uncorrected. Rotation of the cylinder changes the axis of the resultant astigmatism but little, with a maximum inclination of this axis at a certain error in axis position.

It is shown that this behavior of the axis of the resultant astigmatism can be used as a most accurate subjective test for the refinement of the determination of an astigmatic error in conjunction with the astigmatic dial.

Finally, resultant astigmatic errors as produced by the use of the cross cylinder are analyzed in a few examples, and the advantages of this technic are compared with those of rotation of the trial cylinder.

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INFLUENCE OF PONTOCAINE HYDROCHLORIDE AND CHLOROBUTANOL ON RESPIRATION AND GLYCOLYSIS OF CORNEA

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In a series of preliminary studies on the metabolism of the cornea, the oxygen uptake of the human cornea was compared with that of the bovine cornea. The rate of oxygen uptake of the human cornea was insignificantly low. Since the human eye from which the cornea studied was obtained had been removed during local anesthesia with pontocaine hydrochloride, the effect of this drug on the bovine cornea was tested. When a comparable amount of the drug was added to a normally respiring bovine cornea, a considerable decrease in the oxygen consumption resulted. Consequently, we set out to make systematic measurements on the inhibitory effect of this drug, to compare it with other drugs commonly used in the eye and to determine if possible in what portion of the respiratory chain the inhibition occurs.

EXPERIMENTAL TECHNIC

Corneas from bovine eyes were used. The eyes arrived in the laboratory about two hours after the animals were slaughtered. The corneas were excised as near to the limbus as possible and each cornea divided into two approximately equal parts. The fresh weight of a single whole cornea amounted to about 700 to 800 mg. Four half-corneas were introduced into the main compartments of conic Warburg vessels, and Ringer-phosphate solution of a p_H of 7.5 was added. The total volume was made up to 4 cc. and the manometric estimation of the oxygen uptake carried out as usual at 38 C. (Ringer-phosphate solution is made up of 25 cc. of distilled water, 25 cc. of Ringer solution and 5 cc. of half-normal phosphate solution.)

For the estimation of lactic acid the method of Barker and Summerson was used.[1] After observation of the oxygen uptake, the contents of the Warburg cups

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1. Barker, S. B., and Summerson, W. H.: The Colorimetric Determination of Lactic Acid in Biological Material, J. Biol. Chem. **138**:535, 1941.

were transferred into glass mortars, 1 cc. of 15 per cent trichloroacetic acid added to each and the cornea pressed vigorously. The contents of the mortars were then transferred into centrifuge tubes, with the addition of enough distilled water in each tube to bring the volume to 10 cc. The samples were allowed to stand for about fifteen minutes with frequent stirring. Then the solid material was centrifuged off and 1 cc. of the supernatant fluid in each tube removed to another centrifuge tube for further treatment. One cubic centimeter of 20 per cent copper sulfate solution, 8 cc. of distilled water and 1 Gm. of pulverized calcium hydroxide were added to each sample. After a half-hour, during which the samples were well shaken several times, they were centrifuged, and 0.5 cc. of the supernatant fluid was taken for the subsequent color development. In each series a blank and a standard containing 5 micrograms of lactic acid were run and the determination was made with a Klett filter no. 56 in a Klett-Summerson photoelectric colorimeter. The procedure was not affected by the concentrations of pontocaine hydrochloride and of chlorobutanol used in the experiments.

Cytochrome C was prepared according to the method of Keilin and Hartree.[2] The material obtained from six pig hearts was dissolved in about 10 cc. of distilled

TABLE 1.—*Effect of Commercial Pontocaine Hydrochloride Solution on the Oxygen Uptake of Bovine Cornea* *

Cc. of 0.5% Commercial Pontocaine Hydrochloride Solution Added	Concentration, Mols per Liter		Oxygen Uptake 2 Corneas in 30 Minutes, Cu. Mm.	Per Cent Inhibition
	Pontocaine Hydrochloride	Chlorobutanol		
0	.....	.....	81, 81, 80	..
0.125	0.0005	0.0007	81	0
0.16	0.0007	0.0010	65	19
0.25	0.001	0.0015	70, 65	17
0.5	0.002	0.003	32, 31	62
1.0	0.004	0.006	20, 22	75

* Duplicate experiments listed separately.

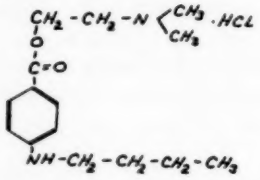
water. The solution contained approximately 1 per cent acetone-precipitable substance. Addition of 0.1 cc. of this solution was enough to raise the oxygen uptake of a cytochrome oxidase preparation to a maximum level of about 200 cu. mm. in twenty minutes per cubic centimeter of the preparation, with phenylenediamine (2 per cent) as substrate. The cytochrome oxidase for this test was obtained in the usual way, by extraction of heart muscle with secondary phosphate solution and precipitation of the cloudy fluid at p_H 4.7. This material was also used for the experiments concerning the inhibition of cytochrome oxidase by pontocaine hydrochloride and served as a source of lactic and malic dehydrogenases, which were used in later experiments. Of this preparation, 0.5 cc. decolorized 5 cc. of 1:20,000 methylene blue solution in three minutes when 0.5 cc. of normal lactate or malate solution, 0.25 cc. of normal sodium cyanide solution as a ketofixative and 2 mg. of a crude cozymase prepared from yeast were added. Without substrate no decoloration occurred within one hour. Corneal epithelium can easily be obtained by scraping the surface of the cornea of the intact bovine eye.

2. Keilin, D., and Hartree, E. F.: Preparation of Pure Cytochrome C from Heart Muscle and Some of Its Properties, Proc. Roy. Soc., London, s.B **122**:298, 1937.

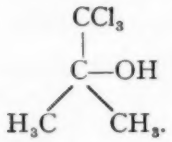
All solutions of the various drugs tested were adjusted to neutrality, and in the experiments with the Warburg technic were added directly to the main compartment of the cups. Per cent inhibition was calculated by comparison with control samples, to which no drugs were added.

RESULTS

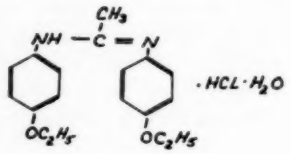
The effect of varying concentrations of commercial pontocaine hydrochloride [3] solution on the oxygen uptake of the cornea is shown in table 1. The commercial solution for ophthalmic anesthesia contains 0.5 per cent pontocaine hydrochloride,



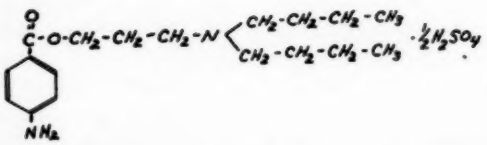
and in addition, as a preservative, 0.5 per cent chlorobutanol,



Each of these substances inhibits corneal respiration independently, but when they are used together in proper concentrations, their effects are additive (table 9). The effects of the local anesthetics phenacaine hydrochloride,



and butyn sulfate,



are similar, butyn being chemically related to pontocaine. A comparison of these substances with several other drugs showed that the inhibitory effect is not limited to local anesthetics (table 2). It can

3. The Winthrop Chemical Co., Inc., supplied the crystalline pontocaine hydrochloride used in this study.

be shown that inhibition of respiration does not directly cause local anesthesia. Soluble pentobarbital (pentobarbital sodium) has no anesthetic effect in the concentrations which depress respiration.[4] Atropine is a more powerful inhibitor of corneal respiration than cocaine. Ephedrine and ethyl carbamate (ethyl urethane) are almost as ineffective as hypertonic salt solution. This last observation was wholly unexpected, since ethyl carbamate has been shown to be an inhibitor of the respiration of the brain,[5] while ephedrine has been found to be a powerful inhibitor of the cytochrome oxidase system of other organs.[6] Nevertheless, the cornea seems to contain a cytochrome oxidase system, since its respiration is inhibited by cyanide (table 3) and by azide (table 4) and since its capacity to oxidize hydroquinone and phenylenediamine is

TABLE 2.—*Per Cent Inhibition of the Oxygen Uptake of Bovine Cornea by Various Drugs*

	Concentration of the Applied Inhibitors in Mols per Liter									
	0.0016	0.003	0.006	0.015	0.03	0.06	0.12	0.25	0.5	1.0
Soluble pentobarbital (pentobarbital sodium)	40	..	73	..	90	..	..	..	..	..
Pontocaine hydrochloride	25	71	77	..	..	..	..	..	..	..
Chlorobutanol	..	38	75	99	..	..	..	..	..	..
Phenacaine hydrochloride	..	17	..	55	60	..	..	..	..	..
Butyn sulfate	..	9	..	38	75	..	..	..	..	..
Atropine sulfate	..	..	20	28	45	..	..	..	..	..
Cocaine hydrochloride	..	..	..	15	21	..	82	..	..	..
Ephedrine hydrochloride	..	..	..	..	6	13	56	..	..	..
Ethyl carbamate (ethyl urethane)	..	..	..	..	..	..	23	33	..	..
Sodium chloride	..	..	..	..	..	10	20	35	37	72

greatly enhanced by the addition of cytochrome C (table 5). This capacity can be demonstrated only with ground cornea (especially epithelium) after normal respiration has been greatly reduced by prolonged dialysis. Intact, respiring corneal tissue shows no increased oxygen uptake after addition of the respective test substances. Similar observations were made by Breusch [7] on lung tissue. The spontaneous oxygen uptake of this tissue is only slightly increased by addition of phenylenediamine, in

4. Dr. Buschke tested the corneal sensitivity of rabbits after local application of soluble pentobarbital.

5. Quastel, J. H.: Respiration in the Central Nervous System, Physiol. Rev. **19**:135, 1939.

6. Philpot, F.: Inhibition of Adrenaline Oxidation by Local Anesthetics, J. Physiol. **97**:301, 1940.

7. Breusch, F. L.: Der Eigenstoffwechsel des Lungengewebes, Biochem. Ztschr. **297**:24, 1938.

spite of its content of cytochrome oxidase.[8] It would seem likely that the accessibility of the system to ephedrine and other agents varies in different organs.

We have no proof that the rather small cytochrome oxidase activity represents the whole oxygen-activating system of the cornea, but there is no reason to believe that another cyanide-sensitive system is present. It was of interest, therefore, to determine whether the inhibitory effect

TABLE 3.—*Inhibition of the Oxygen Uptake of Bovine Cornea by Cyanide*

Cyanide Concentration, Mols per Liter	Oxygen Uptake of 2 Corneas in 60 Minutes, Cu. Mm.	Per Cent Inhibition
0	150	..
6.6×10^{-4}	58	61
6.6×10^{-3}	28	81

TABLE 4.—*Inhibition of the Oxygen Uptake of Bovine Cornea by Azide*

Azide Concentration, Mols per Liter,	Oxygen Uptake of 2 Corneas in 60 Minutes, p_H 7.5; Cu. Mm.	Per Cent Inhibition	Oxygen Uptake of 2 Corneas in 60 Minutes, p_H 6.3; Cu. Mm.	Per Cent Inhibition
0	180	..	125	..
3.8×10^{-5}	148	18	115	6
3.8×10^{-4}	147	18	65	47
3.8×10^{-3}	74	53	39	68
3.8×10^{-2}	52	71	23	81

TABLE 5.—*Demonstration of the Presence of Cytochrome Oxidase in the Corneal Epithelium*

	Oxygen Uptake, Cu. Mm. in 15 Minutes	
	Before Addition of Substrate	After Addition of Substrate
Hydroquinone	17	20
Hydroquinone + cytochrome C (10 mg.)	18	111
Phenylenediamine	18	39
Phenylenediamine + cytochrome C (10 mg.)	20	106

Each manometer cup contained 3 cc. of a dialyzed epithelial cell suspension corresponding to 5 bovine eyes made up in thirtieth normal phosphate buffer, p_H 7.2, and 10 mg. of substrate in the side arm. The results are corrected for the small auto-oxidation.

of pontocaine hydrochloride and chlorobutanol could be attributed to an effect on this enzyme system. Neither the cytochrome oxidase of the corneal epithelium nor that of the pig heart was found sensitive to either of these drugs in concentrations which almost completely depressed the respiration of the whole cornea.

Since we were unable to show any effect of these drugs on the oxygen-activating system of the cornea, we turned our attention to another phase of respiratory metabolism, namely anaerobic glycolysis.

8. Stotz, E.: The Estimation and Distribution of Cytochrome Oxidase and Cytochrome C in Rat Tissues, J. Biol. Chem. **131**:555, 1939.

As a measure of anaerobic breakdown of carbohydrate, we used the manometric determination of acid production in a bicarbonate-containing medium. Even without the addition of substrate, two bovine corneas produce enough acid to make manometric determinations easily possible. The production of anaerobic acid is markedly inhibited by monoiodoacetate and fluoride, as shown in table 6, a fact indicating that the glycolytic system of the cornea is similar to that of other organs.[9] Pontocaine hydrochloride and chlorobutanol were found to be without effect on the anaerobic acid production of the cornea. It follows that the inhibition of respiration produced by these drugs is not due to a lack of supply of the carbohydrate cleavage products which are required for respiration.

In addition, the effect of pontocaine hydrochloride on lactic and malic dehydrogenases prepared from pig hearts was investigated, the enzyme activity being measured by the Thunberg technic. No inhibition of the dehydrogenase systems was observed with concentrations capable of

TABLE 6.—*Effect of Monoiodoacetate and of Fluoride on the Oxygen Uptake and Anaerobic Acid Production of Bovine Cornea*

Reagent Added	Concentration in Mols per Liter	Oxygen Uptake of 2 Corneas, Cu. Mm. in 30 Minutes	Per Cent Inhibition	Acid Production of 2 Corneas, Cu. Mm. of Carbon Dioxide in 30 Minutes	Per Cent Inhibition
Monoiodoacetate	0	80	..	82	..
	1.2×10^{-3}	75	6	14	83
	4.5×10^{-3}	63	21	19	77
Fluoride	10×10^{-3}	70	12	31	62
	40×10^{-3}	59	26	20	76
	160×10^{-3}	34	57	14	83

inhibiting corneal respiration. Quastel[5] has made similar tests with chlorobutanol, reaching similar conclusions.

Evidence has been presented recently supporting the assumption that interposed between the dehydrogenase system, which operates on the products of anaerobic carbohydrate breakdown, and the final oxygen-activating system a series of reversibly oxidizable substances act as carriers between the two systems. Examples of these carriers are the C_4 acid cycle, the citric acid cycle, certain flavoproteins, pyridine nucleotides and possibly other substances. If these are interfered with while all other components of the respiratory metabolism remain normal, respiration will stop and the products of glycolysis, particularly lactic acid, can be expected to accumulate. The results of experiments designed to disclose whether lactic acid accumulates when respiration is inhibited by pontocaine and chlorobutanol are shown in tables 7, 8 and 9. It can be

9. Inhibition of anaerobic glycolysis by iodoacetate without inhibition of oxygen uptake analogous to our own observation has been reported by S. B. Barker, E. Shorr and M. Malam (Studies on the Pasteur Reaction: Effect of Iodoacetic Acid on the Carbohydrate Metabolism of Isolated Mammalian Tissue, J. Biol. Chem. **129**:33, 1939).

seen that except with the highest concentrations of pontocaine hydrochloride the accumulation of lactic acid increases with increasing inhibition of respiration. Pontocaine has some inhibitory action at lower

TABLE 7.—*Effect of Pontocaine on the Oxygen Uptake and the Lactic Acid Content of Bovine Cornea* *

Pontocaine Hydrochloride Concentration, Mols per Liter	Oxygen Uptake of 2 Bovine Corneas, Cu. Mm. per Hour			Per Cent Inhibition, Average	Lactic Acid Content After 1 Hour Incubation, Mg.			Per Cent Increase, Average
	A	B	C		A	B	C	
0	129	147	161	..	0.7	1.1	0.8	..
1.6×10^{-3}	102	127	101	25	1.5	1.2	0.9	38
3.2×10^{-3}	28	47	50	69	2.4	1.6	1.2	61
4.8×10^{-3}	25	32	42	68	2.8	2.2	0.9	88
6.4×10^{-3}	21	36	42	68	0.8	1.9	1.0	42

* Results of 3 experiments, A, B and C.

TABLE 8.—*Effect of Chlorobutanol on the Oxygen Uptake and the Lactic Acid Content of Bovine Cornea* *

Chlorobutanol Concentration, Mols per Liter	Oxygen Uptake of 2 Corneas, Cu. Mm. per Hour			Per Cent Inhibition, Average	Lactic Acid Content After 1 Hour Incubation, Mg.			Per Cent Increase, Average
	A	B	C		A	B	C	
0	115	136	139	..	1.2	0.9	1.0	..
2.7×10^{-3}	72	85	86	38	1.7	1.2	1.1	29
5.4×10^{-3}	50	31	36	70	1.8	1.2	1.4	42
8.1×10^{-3}	14	5	14	92	2.0	1.3	1.6	58
1.1×10^{-2}	0	0	4	99	2.1	1.7	1.9	84

* Results of 3 experiments, A, B and C.

TABLE 9.—*Comparison of the Effect of Pontocaine (1.6×10^{-3} Mols per Liter) and of Chlorobutanol (2.7×10^{-3} Mols per Liter) on the Oxygen Uptake and the Lactic Acid Content of Bovine Cornea* *

Reagent Added	Oxygen Uptake of 2 Corneas, Cu. Mm. per Hour		Lactic Acid Content After 1 Hour Incubation, Mg.	
	A	B	A	B
Control	145	118	1.1	1.3
Pontocaine hydrochloride	108	64	1.6	2.1
Pontocaine + chlorobutanol	30	27	2.1	2.8
Chlorobutanol	127	85	1.5	1.7

* Results of 2 experiments, A and B

concentrations than chlorobutanol but even in maximal concentration produces only 75 per cent inhibition, while chlorobutanol at this concentration gives complete inhibition. Possibly the points of action of these drugs are not identical. Table 9 shows that the effect of the two drugs is additive.

COMMENT

Fischer [10] has shown that the cornea normally can utilize oxygen directly from the air. Thus the respiration of the whole structure can be studied supravitally without slicing or maceration. In fact, wounds of the corneal epithelium have been shown to heal in the isolated organ as long as two days after its removal from the body.[11] This tissue provides, therefore, an unusually satisfactory test object for metabolic studies in which normal structure must be maintained. Perhaps nowhere is maintenance of normal structure more important than in the domain of pharmacology, for the ability of a drug to reach the locus of its action is at least as important as its ability to produce an effect once it has gained access. In the experiments reported here, two examples were encountered in which the intact organ was unaffected by a drug known to have strong effects on isolated enzyme systems. The drugs were ethyl carbamate (ethyl urethane) and ephedrine.

In view of the fact that studies on the metabolism of the cornea, in regard not only to its pharmacology but to its physiology and pathology promise a rich reward in new knowledge, it is surprising that few such studies have been reported.[12] Only Kohra [13] has previously measured the respiration and glycolysis of the cornea. The somewhat higher figures which he obtained, when computing on the basis of milligrams of dry weight, are possibly to be attributed to a species difference, since he used rabbits, whose corneas contain relatively less of the metabolically inert stroma than do those of cattle.

Confirming and extending Kohra's results, we can conclude that the metabolism of the cornea includes the phases of glycolysis, dehydrogenation and oxygen activation and a number of intermediating carriers. Pontocaine and chlorobutanol were found to have no effect on glycolysis, on dehydrogenation of lactic and of malic acid or on oxidation of cytochrome C. Nevertheless, these drugs inhibit respiration and lead to an accumulation of lactic acid [14] in the tissue. These two phenomena could be explained simultaneously if it were assumed that the

10. Fischer, F. P.: Ueber den Gasaustausch der Hornhaut mit der Luft, Arch. f. Augenh. **102**:146, 1930.

11. Puckovskaya, N.: Regenerative Capacity of Corneal Epithelium, Vestnik oftal. **17**:23, 1940; abstracted, Zentralbl. f. d. ges. Ophth. **46**:531, 1941.

12. Weekers, R.: Biochimie de la cornée normale et pathologique, Ophthalmologica **100**:136, 1940. Süllmann, H.: Biochemie des Auges, ibid. **96**:37, 1938. Fischer, F. P.: The Biochemistry and Metabolism of the Eye, in Ridley, F., and Sorsby, A.: Modern Trends in Ophthalmology, New York, Paul B. Hoeber, Inc., 1940.

13. Kohra, T.: Ueber den Stoffwechsel der Hornhaut, Acta Soc. ophth. jap. **40**:125, 1936.

14. The significance of the designation "lactic acid" depends on the specificity of the method of determination. The high specificity of the employed method was discussed in the paper of Barker and Summerson.[1]

drugs attack the system intermediating between lactic acid dehydrogenase and cytochrome oxidase. Alternative hypotheses that these drugs enhance aerobic glycolysis (they have no effect on anaerobic glycolysis) or that they inhibit the resynthesis of lactic acid into dextrose cannot be excluded with certainty. However, Michaelis and Quastel [15] have shown that chlorobutanol inhibits the hydrogen transport of a system consisting of lactic acid, lactic dehydrogenase, coenzyme, coenzyme factor, cytochrome C and cytochrome oxidase. The oxidation of lactic acid by this system is not inhibited if methylene blue is available as hydrogen acceptor. Similarly, the oxidation of succinate, hydroquinone, etc., by this system is not inhibited. Quastel concluded that narcotics interfere with some carrier between the dehydrogenase system and the cytochrome system or with a part of the cytochrome system not required for the oxidation of the common test substrates.

The extent to which the decreased oxygen consumption and the increased lactic acid production might be correlated can be apprehended from the following evaluation of our results. By addition of pontocaine hydrochloride or chlorobutanol to two corneas an excess of about 1 mg., equivalent to 0.01 millimol of lactic acid, is produced in one hour. The decrease of oxygen uptake under the same conditions amounts to about 100 cu. mm., which is equivalent to 0.0045 millimol of oxygen. This indicates that the consumption of one oxygen atom corresponds to the disappearance of approximately one lactic acid molecule.

Our presentation has been based on the assumption that the respiration depends on production and oxidation of lactic acid. However, working with a tissue with unexplored metabolic properties, one cannot exclude the possibility that the accumulation of lactic acid is due to the interruption of a metabolic pathway which has nothing in common with the direct production and oxidation of lactic acid itself.

SUMMARY

1. Pontocaine and chlorobutanol, soluble pentobarbital, phenacaine, butyn, atropine and cocaine in varying degree inhibit the oxygen uptake of the bovine cornea.

2. Ephedrine and ethyl carbamate (ethyl urethane) are without effect.

3. An oxygen-activating system, presumably cytochrome oxidase, and anaerobic glycolysis of the cornea are practically unaffected by pontocaine and chlorobutanol.

4. The aerobic accumulation of lactic acid, however, is greatly enhanced by these two drugs.

Johns Hopkins Hospital.

15. Michaelis, M., and Quastel, J. H.: The Site of Action of Narcotics in Respiratory Processes, Biochem. **35**:518, 1941.

THE CORNEA

V. PHYSIOLOGIC ASPECTS

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Previously we have presented experimental data on the permeability and the swelling characteristics of the cornea.[1] The purpose of the present report is to integrate these experimental findings into a theory of corneal function and to obtain thereby an explanation for some of the properties that are apparently unique to the cornea.

1. SYNOPSIS AND REVIEW

Corneal pieces show an extraordinary capacity to swell when immersed in various aqueous solutions, including blood serum and aqueous humor, regardless of the tonicity of the solution, the nature of the solvent or the hydrogen ion concentration. This property of imbibing fluid over and above the normal content, or, in other words, this characteristic of being maintained normally in a deturgesced state, distinguishes the cornea, in general, from other tissues. It is especially remarkable in comparison with the sclera, for scleral pieces swell little or not at all in solutions which result in a corneal swelling of several hundred per cent; yet in other respects the stroma of the sclera is essentially similar to that of the cornea.

Despite this seemingly unique characteristic of the normal cornea, there has been little speculation on the part of investigators to account for it. Leber's [2] thesis has been almost unanimously accepted without reservation. Leber had observed that removal of the corneal endothe-

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1. (*a*) Cogan, D. G., and Kinsey, V. E.: The Cornea: I. Transfer of Water and Sodium Chloride by Osmosis and Diffusion Through the Excised Cornea, Arch. Ophth. **27**:466 (March) 1942; (*b*) II. Transfer of Water and Sodium Chloride by Hydrostatic Pressure Through the Excised Cornea, ibid. **27**:696 (April) 1942. (*c*) Kinsey, V. E., and Cogan, D. G.: The Cornea: III. Hydration Properties of Excised Corneal Pieces, ibid. **28**:272 (Aug.) 1942; (*d*) The Cornea: IV. Hydration Properties of the Whole Cornea, ibid. **28**:449 (Sept.) 1942.

2. Leber, T.: Studien über den Flüssigkeitswechsel im Auge, Arch. f. Ophth. (pt. 2) **19**:87, 1873; Die Circulations- und Ernährungsverhältnisse des Auges, in Graefe, A., and Saemisch, E. T.: Handbuch der gesamten Augenheilkunde, ed. 2, Leipzig, Wilhelm Engelmann, 1903, vol. 2, pt. 2.

lium resulted in a swelling of the cornea, presumably by imbibition of aqueous, and inferred that the normal cornea was not swollen because of an impermeability of the endothelium. Accordingly, the endothelium is represented in current textbooks as a "water-tight" membrane which, while allowing transfer of many dissolved substances (atropine, etc.), does not permit the passage of water.[3] The chief evidence for this conception is Leber's experiment, but, as has been pointed out,[1d] his results can be explained by a theory which is seemingly more tenable. Moreover, there are several major objections to the conception (Leber's) that maintained deturgescence of the cornea depends on a water-tight membrane. It does not account, for instance, for the absence of imbibition of fluid from the limbal plexus, where there is no membrane separating the corneal stroma from a source of fluid. Also, it has been contradicted by experiments which showed that water passes relatively freely through the cornea either in the presence of an osmotic force or by simple diffusion.[1a] Finally, it would be an exceptional membrane that would allow the passage of dissolved substances but not water.

The absence of swelling in vivo might be assumed to be due to such physical forces as the intraocular pressure or, as has been suggested by Virchow,[4] the structural compactness of the cornea. Neither of these proposals explains the difference in turgescence between the cornea and the sclera, and both are contradicted by the experimental results.

It thus appears that previously there has been no tenable explanation offered to account for the maintenance of the relatively deturgesced state of the normal cornea.

In the earlier studies on corneal permeability we observed that corneas which had been tied on the ends of tubes did not swell when water was being transferred through them by osmosis. Elimination of maintained osmotic force on the two sides of the cornea by adjusting the tonicity of the solutions or by removing the semipermeable membranes —the epithelium and the endothelium—resulted in swelling of the cornea. At first it seemed paradoxic that when there was a net transfer of water through the cornea no swelling occurred, but when no such transfer was demonstrable the cornea became swollen. The only explanation appears to be as follows: In the presence of the osmotic force water is abstracted from the cornea as it becomes available in

3. Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1932, vol. 1, p. 472.

4. Virchow, H.: Mikroskopische Anatomie der äusseren Augenhaut und des Lidapparates, in Graefe, A., and Saemisch, E. T.: Handbuch der gesamten Augenheilkunde, ed. 2, Leipzig, Wilhelm Engelmann, 1910, vol. 1, chap. 2, sect. 2., p. 275.

the stroma. In the presence of large osmotic forces, such as were present when 5 per cent sodium chloride solution was in contact with the epithelial side of the whole cornea and water was in contact with the endothelial side, the cornea was kept in a state of deturgescence significantly greater than normal. The normal state of hydration was found to be approximated experimentally when an osmotic difference of 0.7 per cent sodium chloride existed between the front and the back of the cornea. It may be concluded, therefore, that a state of deturgescence comparable in magnitude to that existing normally may be maintained under the conditions of the experiment by appropriate osmotic forces.

There was a fundamental difference, however, between the conditions of the experiments on the excised corneas and those existing for the intact eye; namely, the endothelium was functionally destroyed by the manipulation of tying the cornea onto the tube. Hence these conclusions from experiments on the cornea-tube preparations can be applied only to the specific conditions wherein the epithelium is the sole semipermeable membrane and the direction of fluid transfer is toward the anterior surface of the cornea. But there is abundant evidence that the endothelium, while more susceptible to trauma, is a semipermeable membrane, as is the epithelium, and is similarly capable of keeping the cornea deturgesced under the proper conditions.

The evidence for semipermeability is less direct for the endothelium than for the epithelium and less amenable to quantitative measurement. Yet all the permeability characteristics of the epithelium can be shown to hold at least qualitatively for the endothelium also. Thus fluid transfer through the cornea and the maintenance of a state of corneal deturgescence can also be demonstrated when the endothelium is acting as a semipermeable membrane. The experiment was carried out by first removing the epithelium from an enucleated eye and placing the corneal portion of the eye in distilled water. So long as the endothelium was intact and the aqueous was hypertonic to the fluid on the outside of the eye, the intraocular pressure rose, indicating movement of water into the eye, and the cornea remained partly deturgesced. If the endothelium was first removed this rise in pressure did not occur and the cornea became swollen. This experiment showing the semipermeability of the endothelium was analogous to that in which the semipermeability of the epithelium was demonstrated with the cornea-tube preparations when the epithelium was in contact with a hypertonic fluid.

Another experimental result indicating the similarity of the epithelium and the endothelium as regards their permeability characteristics was the peeling off of either membrane when the fluid on its nonstromal side was hypotonic to that on its stromal side. In the case of the

epithelium this result was manifested by an edema with subsequent formation of bullae. The corresponding endothelial condition was produced by reversing the conditions which elicit it with the epithelium, but more care was necessary in the manipulation: The epithelium was first removed, and the enucleated eye was held in a clamp, corneal side upward. A cannula was inserted through the optic nerve into the eye and connected with a reservoir of water designed to maintain a constant intraocular pressure of approximately normal magnitude. A small glass tube with a flared end was then placed in contact with the cornea and pressed against it with just sufficient force to prevent leakage at the cornea-tube junction. The tube was then filled with 5 per cent sodium chloride solution. This procedure was carried out with a series of eyes, and at five minute intervals one eye was removed for slit lamp study. In about fifteen minutes most of the corneas showed a separation of the posterior surface (endothelium), and the torn membrane attached at various points to the back surface of the cornea projected into the anterior chamber. While the endothelium lost its character as a continuous membrane much sooner than the epithelium did under analogous conditions and burst before producing large bullae, the process and the ultimate result were essentially the same.

The cornea may thus be shown to have a semipermeable membrane on both its anterior and its posterior surface.

2. THEORY OF FLUID MOVEMENT

In the presence of sufficiently hypertonic fluid in contact with the epithelial or the endothelial surface, the cornea may be kept experimentally in a state of deturgescence analogous to its normal condition. The situation in vivo can at present only be inferred, but the maintained deturgescence of the normal cornea apparently can be explained only by assuming that similar differences in osmotic pressure occur between the corneal fluid on the one hand and the fluids in contact with the corneal surfaces on the other. Actual measurements of the osmotic pressures have been few. But there is some evidence that the fluids on the surfaces of the cornea are actually hypertonic to the corneal fluid, for, while the osmotic pressure of the latter cannot be greater than that of the blood (being in equilibrium with the limbal fluid), that of the tears [5] and of the aqueous [6] have been reported to be greater

5. Weiss, O.: Der intraokulare Flüssigkeitswechsel, Ztschr. f. Augenh. **25**: 1-14, 1911.

6. Benham, G. H.; Duke-Elder, W. S., and Hodgsen, T. H.: Osmotic Pressure of Aqueous Humor in Normal and Glaucomatous Eye, J. Physiol. **92**: 355-360, 1938. Roepke, R. R., and Hetherington, W. A.: Osmotic Relation Between Aqueous Humor and Blood Plasma, Am. J. Physiol. **130**:340-345, 1940.

than that of the blood. It must be remembered, however, that such quantitative comparisons are difficult to make, for normal corneal fluid is practically impossible to obtain in sufficient amounts; the same is true for that portion of the tears which overlies the cornea and which for our purposes is the only significant part. So far as evaporation is concerned, the osmotic pressure of the tears would, of course, be increased.

Granted that the fluids on the surfaces of the cornea are hypertonic to the corneal fluid and that, as has been shown, the epithelium and the endothelium are effective barriers to the physiologic electrolytes, most if not all of the substances entering the cornea must come from the limbal vascular plexus. Thence these substances diffuse centripetally along the lamellas and toward the surfaces. Because of the osmotic forces at these surfaces, there is continuously a net loss of water from the cornea. As a result the cornea is being continuously deturgesced and the state of corneal hydration at any one time will depend on the osmotic forces on the one hand and the availability of fluid and the imbibatory power of the corneal stroma on the other.

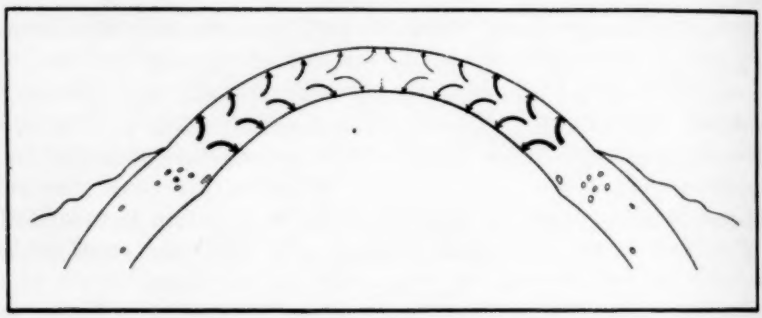
As the removal of fluid occurs over the relatively large area of the combined anterior and posterior surfaces (approximately 2 sq. cm.), while the source of fluid is limited to the relatively small limbal collar (approximately 0.4 sq. cm.), it is probable that any reasonable increase in the availability of fluid, even by moderate vascularization of the cornea, can be compensated by the relatively more efficient operation of the deturgescing forces. As the imbibatory power of the stroma is presumably constant, variations in the state of hydration will, therefore, be determined under normal conditions by the forces acting at the corneal surfaces. Decreasing or eliminating the osmotic forces through removal of the semipermeable membranes—endothelium and epithelium—results in swelling of the cornea, while increasing the osmotic forces by use of hypertonic solutions results in correspondingly greater deturgescence of the cornea. The normal state of hydration represents, therefore, an equilibrium between the inherent imbibatory capacity of the corneal stroma and the osmotic forces acting at the corneal surfaces.

The theory of fluid movement described may be represented by the accompanying sketch, in which the direction of the arrows indicates the net movement of water.[7] The dissolved substances might also be assumed to follow similarly the course of the arrows; however, since there is no appreciable loss of these substances through the surface membranes, they must establish an equilibrium by diffusing in both

7. A diagram bearing some similarity to the one presented but based on entirely different considerations and applying only to the posterior corneal surface was proposed by Grüber.[9a]

directions, arising and being ultimately eliminated at the limbal plexus. The local concentrating effect of the dissolved substances through selective loss of water at the surfaces may account for the laminas of increased chlorides which have been reported to occur just beneath the epithelium and the endothelium.[8]

The greatest amount of net fluid movement would be expected to occur adjacent to the limbus, and the amount would be progressively less toward the center of the cornea. This variation is represented in the sketch by the thickness of the arrows. Such a difference in fluid movement in the different portions of the cornea is borne out in experimental staining of the cornea with dyes[9] and in such clinical conditions as hematogenous pigmentation, in which clearing occurs from the periphery toward the center.



Schematic drawing to illustrate the theory of fluid movement through the cornea. The arrows indicate the direction of flow, and the density of the arrows from the periphery to the center indicates the relative amount of fluid movement. The amount of movement toward the anterior and toward the posterior surface, while shown by the density of the arrows to be equal, is not known.

On the basis of this theory we may say that the fundamental difference between cornea and sclera, so far as turgescence is concerned, lies in the fact that the former is kept continuously deturgesced by means of its semipermeable membranes. The sclera, having no such

8. Fischer, F. P.: Ueber die Permeabilität der Hornhaut und über Vitalfarbungen des Bulbusabschnittes mit Bemerkungen über die Vitalfarbung des Plexus chorioideus, Arch. f. Augenh. **100-101**:480, 1929.

9. (*a*) Grüber, R.: Beiträge zur Kenntnis der Hornhaut-Circulation, Arch. f. Ophth. (pt. 4) **40**:25-64, 1894. (*b*) Laqueur: Ueber die Durchgängigkeit der Hornhaut für Flüssigkeit, Vorläufige Mittheilung, Centralbl. f. d. med. Wissensch. **10**:577, 1872. (*c*) Ridley, F.: An Experimental Investigation into the Intraocular Pressure and Drainage of Aqueous Humor: I. The Drainage Path of Aqueous Humor, Tr. Ophth. Soc. U. Kingdom **50**:268-309, 1930.

membranes,[10] is normally swollen to its maximum in physiologic solutions. This fundamental difference between cornea and sclera suggests that the semipermeable membranes, with their effect on fluid movement, may serve the following peculiar requirements of the cornea.

3. DETURGESCENCE AND TRANSPARENCY

It has always been a source of amazement that the conspicuous optical difference which exists between cornea and sclera has never been shown to have any histologic counterpart. The stroma of one merges into that of the other at the limbus without any abrupt transition corresponding to the change from transparent to opaque portions of the corneoscleral coat. That the swelling and optical peculiarities of the cornea might be correlated has been suggested several times. It has long been known that when the cornea takes up water it becomes opaque [11] and, on the other hand, that when the sclera loses water it becomes transparent.[12] The optical differences between the cornea and the sclera would therefore appear to be associated with their relative states of hydration.

Thus, in order for the cornea to remain transparent it must be maintained in a deturgesced state; it is so maintained, according to the theory previously advanced, by continuous removal of water through differences in the osmotic pressure. The effectivity of the osmotic pressure in turn depends on the presence of the semipermeable membranes. At the limbus, where these membranes terminate, the stroma becomes relatively hydrated and opaque, thus accounting for the abrupt optical transition for which there is no histologic counterpart. Removal or destruction of one of the semipermeable membranes, as in Leber's experiment, results in swelling and opacity of the cornea. The cornea then approaches the sclera in its optical properties. The function of water removal such as we have described, by which the cornea is maintained in a deturgesced state, may, therefore, be thought to serve the optic requirements of the cornea.

While it is evident that relative dehydration of the cornea results in transparency—a fact which is subject to experimental confirmation—the means by which this is brought about can only be inferred. Certain is it that a structure in which there are sufficient reflecting sur-

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10. The conjunctiva is not a semipermeable membrane with respect to sodium chloride.[1b]

11. Leber,[2] chap. 8, p. 357. Virchow.[4]

12. Fischer, F. P.: Die medizinischer Kolloidlehre im Beziehung zum Auge, Zentralbl. f. d. ges. Ophth. **27**: 657, 1932. Verrijp, C. D., and Duyster, C. B.: Observations on Double Refraction, Nederl. tijdschr. v. geneesk. **79**:1986-1988, 1935; abstracted, Zentralbl. f. d. ges. Ophth. **34**:249, 1935.

faces, by reason of different refractive indexes of the constituent parts, will not be transparent. Yet despite the relative transparency of the cornea, this tissue is reported to have a structural component and a fluid component which do have different refractive indexes.[13] It would be expected, therefore, that the cornea could approximate optical homogeneity only by keeping one of these components—in this case the fluid—at a minimum. This conception is consistent with the old observation that the cornea contains an extraordinarily small amount of interstitial fluid.[14] On this basis further removal of fluid from the cornea would be expected to increase corneal transparency further. Such is indeed the case, for if the epithelial surface is bathed for some time with a hypertonic solution the cornea becomes distinctly clearer than normal. On the other hand, accumulation of fluid in the cornea as a result of the taking up of water causes the cornea to become opaque through increase in the anisoindicial constituents.

Further evidence that removal of the water normally present in the cornea increases its optical homogeneity consists of a characteristic variation in what might be called the "stromal stretching" reaction with different degrees of hydration. The stretching reaction may be elicited by squeezing the enucleated eye or otherwise raising the intraocular pressure. The normal cornea then becomes cloudy. If the cornea is appreciably dehydrated beforehand, as by placing 5 per cent sodium chloride solution on the outside of the cornea, the clouding can no longer be elicited even with relatively high pressure, whereas when the cornea is abnormally hydrated, as by allowing an enucleated eye to remain unfixed for twenty-four hours, the clouding can be produced with slight pressure. There is no universally accepted explanation for this clouding phenomenon on pressure, but one of the most plausible hypotheses is that of Verrijp,[15] in which fluid is assumed to be expressed from the structural components into the interstices, thereby producing laminas of different refractive indexes with consequent corneal opacity. The variations of the clouding reaction with different degrees of hydration would appear to be consistent with this thesis and at the same time support the idea that the fluid component of the cornea, having a different refractive index from the structural component, must be largely removed for the cornea to remain optically homogeneous.

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13. Schiøtz, H. A.: Optical Properties of the Cornea, Nord. med. Ark. **14** (no. 28):1-48, 1882. Verrijp, C. D.; Duyster, C. B., and Ouwejan, A. J.: Corneal Opacity, Nederl. tijdschr. v. geneesk. **80**:2379-2384, 1936; abstracted, Zentralbl. f. d. ges. Ophth. **37**:158, 1937.

14. Fuchs, E.: Ueber die traumatische Keratitis, Virchows Arch. f. path. Anat. **66**:401-447, 1876.

15. Verrijp, C. D.: Edema of Cornea and Lens, Nederl. tijdschr. v. geneesk. **81**:2978-2983, 1937; abstracted, Zentralbl. f. d. ges. Ophth. **37**:394, 1937.

4. FLUID DYNAMICS OF THE CORNEA AND METABOLISM

While the method of water movement through the cornea as described maintains transparency, it is probably also of some metabolic significance. The cornea is an avascular structure and has never been shown to have lymphatics. It has been generally assumed that nutritive material is supplied to the cornea only by diffusion from the limbus; now it seems likely that in addition to any diffusion, the movement of water as described insures a continuous circulation for the transfer of oxygen and other dissolved material from the blood to the cornea.

SUMMARY AND CONCLUSIONS

In previous reports experimental data have been presented showing, first, that the cornea has on its anterior and on its posterior surface a membrane which is semipermeable with respect to sodium chloride and, secondly, that the intact cornea may be maintained in a state of relative deturgescence similar to that existing normally by having a hypertonic salt solution in contact with its anterior or its posterior surface.

A theory of fluid movement is presented according to which water is held to be abstracted continuously from the anterior and the posterior surface by osmotic forces. The resultant state of hydration represents an equilibrium between the osmotic forces at the corneal surfaces and the imbibatory power of the corneal stroma. As the epithelium and the endothelium are the semipermeable membranes, they are requisite to the maintenance of corneal deturgescence.

Deturgescence is in turn essential for transparency and constitutes the significant physiologic difference between cornea and sclera, causing the one to be relatively transparent and the other relatively opaque.

The continuous loss of water from the surfaces of the cornea, as stated to occur according to the present theory, provides a circulation for the cornea which may facilitate the transfer of oxygen and other metabolic substances from the blood to the avascular tissues.

243 Charles Street.

DEVELOPMENT OF HUMAN EYE AT FIVE AND FIVE-TENTHS MILLIMETER EMBRYONIC STAGE

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It is rare to obtain an embryo of small size that is well preserved. Such an opportunity was presented to me in the specimen to be described. Many interesting features of the early embryonic development of the eye were clearly seen in serial sections.

The embryo was obtained through Dr. M. A. Goldberger, of the department of gynecology at Mount Sinai Hospital. It was taken directly from the uterus at the time hysterectomy for fibroids was performed, thirty-two days after the onset of the last menstrual period. It therefore could not have been more than 3½ weeks old. It was immediately placed in 10 per cent solution of formaldehyde. With its membranes it measured 7 millimeters from end to end, but microscopic sections later indicated a development usually ascribed to the 5.5 mm. stage.[1] This is probably the more accurate measurement.

The embryo was fixed in 10 per cent solution of formaldehyde for three weeks. It was then dehydrated in alcohol of different concentrations from 30 per cent to 70 per cent and embedded in paraffin. Sections were cut 6 microns thick. Thinner sections are too friable to handle. The slides were stained with hematoxylin and eosin.

Figure 1 is a photograph of the embryo with the membranes and yolk sac still attached. The embryo was not removed from the surrounding tissue because of its small size and the fear that it might be damaged by too much handling. Being colorless and semitransparent, it did not photograph well; nevertheless, a fairly good outline can be made out inside the amniotic sac. It is curved to form a semicircle with the head on a level with the thorax.

Figure 2 is photomicrograph of a transverse section showing both eyes and the forebrain, from which they are derived. The eyes at 5.5 mm. are at an angle of approximately 180 degrees. The single section shows the two eyes at the same time. This is a matter of great interest, because at this stage the eyes are practically at the side of the head. Later on, with the development of the mesoderm behind and lateral to the eyes, especially of the maxillary tissues, they eventually turn

From the laboratories and the ophthalmologic division of Mount Sinai Hospital.

1. Mann, I.: Development of the Human Eye, New York, The Macmillan Company, 1928.

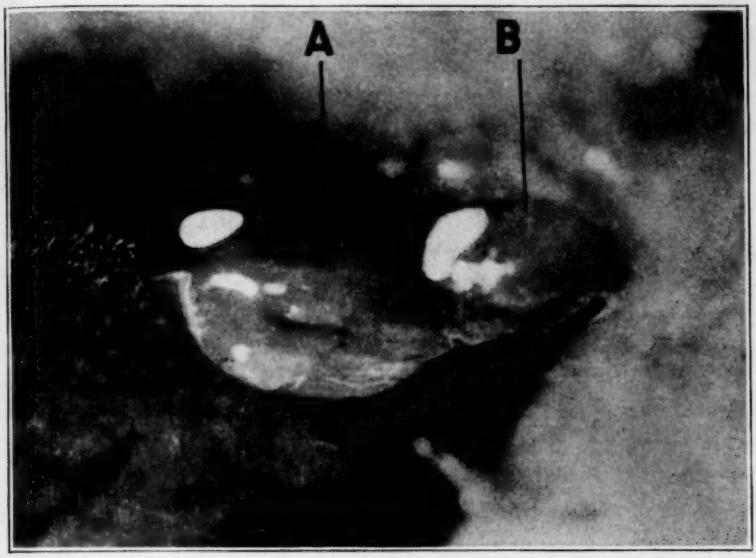

Fig. 1.—Photograph of a 5.5 mm. embryo: *A*, embryo curved like a semicircle with the head on a level with the thorax; *B*, yolk sac.

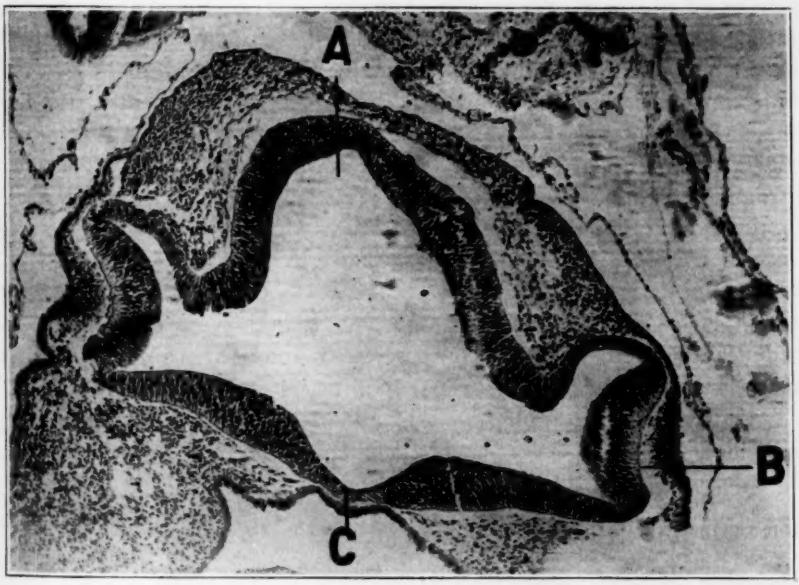

Fig. 2.—Transverse section through the forebrain and the optic vesicle: *A*, cavity of the forebrain; *B*, optic vesicle; *C*, recessus opticus. The cavity of the forebrain is continuous with the cavity of the optic vesicle.

forward, so that the optical axes and the orbit form an angle of 45 degrees. Failure to turn forward results in a condition known as hypertelorism.[2] Failure in development of the midline structures, such as the nose and the ethmoidal and sphenoidal sinuses, will result in fusion of the two eyes, either in part or in whole, giving the anomaly known as cyclops, or the single median eye.[3] Most important of all, however, is the fact that on the forward rotation of the eyes and the orbit depends the development of binocular vision, stereopsis and fusion. The section also demonstrates convincingly the intimate relationship between the eye and the forebrain and illustrates the significance of the expression that the vertebrate eye is a cerebral eye. The cavity of the forebrain is continuous with the cavity of the optic vesicle. The base of this portion of the forebrain forms a depression known as the recessus opticus, which will eventually become filled with nerve fibers and develop into the optic chiasm.

Figure 3 is a somewhat higher-powered picture of the optic vesicle. Here is seen the very beginning of invagination of the optic vesicle. Invagination is an inherent function of the vesicle[4] and apparently is not due to any outside stimulus, such as the proximity of the lens plate. In fact, the reverse is believed to be true, that the lens plate will develop as a result of the presence of the optic vesicle.[5] It should also be noted that the upper part of the vesicle is a little further advanced in development than the lower part. The lower half is phylogenetically newer and younger than the upper half. It is retarded slightly in man but more so in vertebrates lower in the scale of development.[6] Although this fact is not apparent in the section, invagination affects not only the lateral parts of the vesicle but the lower part as well. The lower invagination extends from the margin of the optic vesicle through the stalk up to the forebrain. The optic stalk here is very short and thick. On cross section it would be a hollow tube lined by a single layer of neural epithelium. At this stage the eye is known as the primary optic vesicle, which is beginning to form the secondary optic vesicle, or cup. The outer layer of the optic cup will eventually become the pigment epithelium of the retina, while the inner layer will become the definitive retina.

The next illustration, figure 4, is a photograph of a semidiagrammatic clay model of the optic vesicle at this stage. The model illustrates more

2. Grieg, D. M.: Hypertelorism, Edinburgh M. J. **31**:560, 1924. Berliner, M., and Gartner, S.: Hypertelorism, Arch. Ophth. **24**:691 (Oct.) 1940.

3. Mann, I.: Developmental Abnormalities of the Eye, New York, The Macmillan Company, 1937, p. 61.

4. Maximow (1925), Strangeway and Fell (1926) and Hoadley (1924), cited by Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1932, vol. 1, p. 324.

5. Lewis and Spemann, cited by Mann,[1] p. 23.

6. Mann,[3] p. 12.

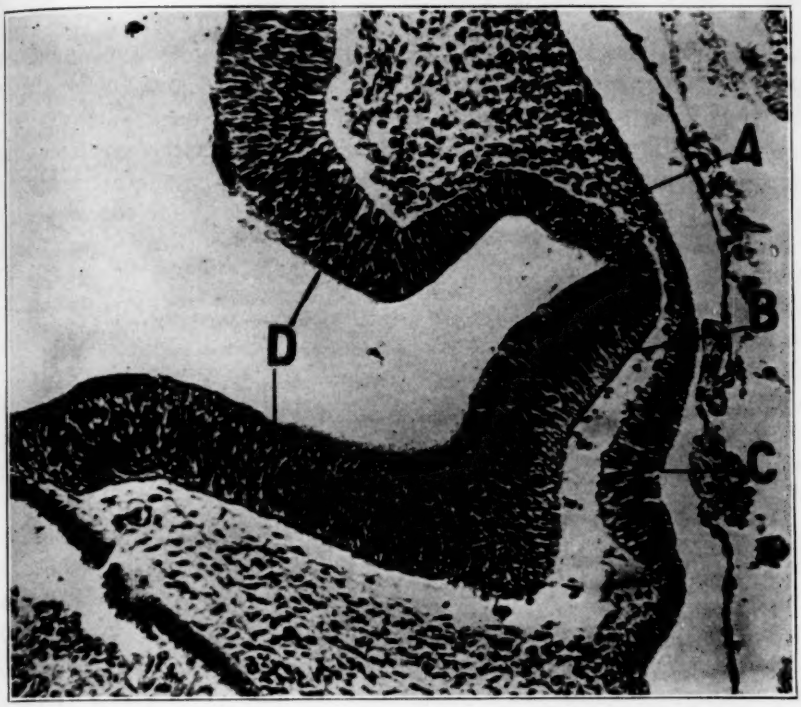

Fig. 3.—The primary optic vesicle just beginning to invaginate to form the optic cup: *A*, outer layer of the optic vesicle; *B*, inner, or retinal, layer; *C*, lens plate; *D*, optic stalk.

Fig. 4.—Semidiagrammatic clay model to show invagination of the primary optic vesicle laterally and from below; *A*, fetal fissure.

clearly than a single serial section can the method by which invagination occurs in two places, laterally and from below. The invagination from below is known as the fetal fissure.

Briefly, the purpose of invagination is to convert the eye from the simple noninverted eye of the lower invertebrates[7] to the more highly specialized inverted eye of the vertebrates. It allows for the exposure of a large area of retina to light stimuli, even though these stimuli come through a small pupil. Also, it permits the sensitive area of the retina, the rod and cone layer, to come in contact with the pigment layer where a separate circulation is developed from surrounding mesoderm, the choriocapillaris. The fetal fissure has a double function. Primarily, it serves as a means whereby the nerve fibers of the ganglion cells of the retina may get back to the brain. Secondly, it allows for the entrance of mesodermal vascular tissue, the hyaloid artery, into the interior of the eye.

Figure 5 is a high power view of the retina showing the earliest stage of retinal development. Here two layers are distinguishable, a nucleated layer and a marginal non-nucleated layer. The nucleated cells form the primary neuroblastic epithelium. From these cells will ultimately come all the different types of cells that make up the retina; the rod and cone cells; the association cells, such as the bipolar and the amacrine cells; the ganglion cells, and the Müller cells. The last-named are the supporting cells of the retina. They send fibers to the inner and outer margins of the retina, forming, by the union of their foot plates, the internal and the external limiting membrane, respectively. This principle is true throughout the body, where the structural framework is laid down before the more highly specialized cells appear. Some of the spindle-shaped cells can be made out on this slide. That a cell is attaining its specialized function is indicated by a change in the shape of the nucleus. The early undifferentiated cells such as those seen here all have oval nuclei. As the cell function becomes more specific, its nucleus becomes round or kidney bean–shaped. Mitotic figures can be seen among the nucleated cells of the retina. This is the stage in which the retina is that portion of the eye which is developing most rapidly.

In front of the optic vesicle is that part of the surface ectoderm which is to form the lens. It is known as the lens plate. Its cells show signs of differentiation. Elsewhere they are cuboidal in shape, but here they are becoming elongated and cylindric. The depression on the lens plate at the junction of the upper two thirds and the lower third is the lens pit. From the lens plate, a hollow vesicle will develop which will

7. Mann,[1] p. 9.

eventually become the lens. Between the retina and the lens plate, numerous fine protoplasmic projections can be made out. These appear to act as a bond between the surface ectoderm and the retina. Also, in this space a few mesodermal cells are seen. These are derived from the surrounding paraxial mesoderm and are vascular in type. These

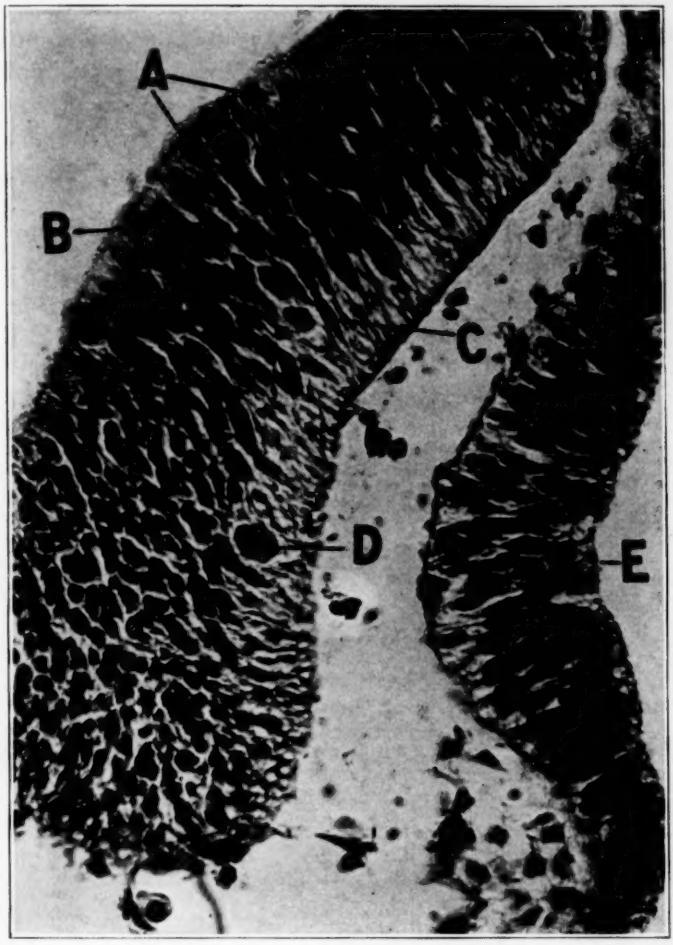

Fig. 5.—High power view of the retinal layer of the optic vesicle: *A*, mitotic figures; *B*, oval nucleus of undifferentiated neuroblastic cell; *C*, Müller fiber cell; *D*, cross section of a retinal capillary; *E*, lens plate forming the lens pit.

three structures, namely the protoplasmic elements from the retina and those from the surface ectoderm and the mesodermal vascular cells, combine to form what is known as the primary vitreous. At this stage

the vitreous is composed of three elements, neural ectoderm, surface ectoderm and mesoderm.

The blood supply to the eye at the 5.5 mm. stage cannot be shown in its entirety in separate sections. A model of the eye is necessary for demonstration. Figure 6 is a photograph of a semidiagrammatic clay model. The main trunk is the carotid artery, which goes upward temporally to the optic stalk and then curves over the stalk to go nasally to the floor of the forebrain. Branches of the carotid artery proceed to the optic vesicle along the line of the fetal fissure below and around the margin of the invaginating optic vesicle in front. This is the vascular mesoderm between the lens and the retina seen in figure 5. At this early

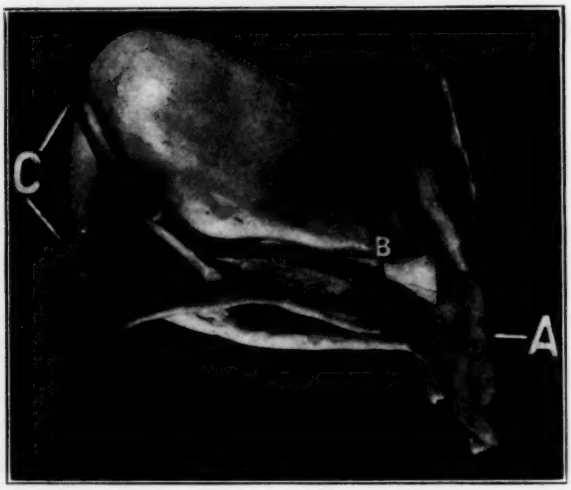

Fig. 6.—Semidiagrammatic clay model showing blood supply to the optic vesicle: *A*, carotid artery; *B*, branch to fetal fissure; *C*, branches to the margin of the optic vesicle.

stage the blood vessels, even the arteries, are thin-walled capillaries composed of a single layer of endothelial cells.

Figure 7 is similar to figure 5, but the section is on a slightly higher level. It is presented in order to demonstrate an interesting feature of the retinal circulation. The retina, like other parts of the central nervous system, is invaded by small capillaries. Such a capillary is shown here containing three nucleated red blood cells. A similar capillary is seen in figure 5 in cross section. These capillaries disappear after the 7 mm. stage, and the optic vesicle gets its blood supply only from the hyaloid artery. Of late these retinal capillaries have taken on an added significance. A theory has been advanced that angiomatosis

retinae, a disease which affects the brain as well as the retina (von Hippel-Lindau disease), may be due to the retention of these capillaries and their continued growth as a compensatory mechanism in regions where the normal retinal circulation has failed to develop.[8]

Fig. 7.—High power view of the retinal layer of the optic vesicle, showing capillary vascularization; *A*, small capillary with nucleated red blood cells. This is a transient phase of retinal circulation.

Many of the structures of the adult eye are not visible at this stage. There is no evidence of extraocular muscles, sclera or choroid, except

8. Junius, P.: Zur Frage der Angiomatosis retinae. Ergebnisse und Folgerungen, Klin. Monatsbl. f. Augenh. **91**:747, 1933.

for the surrounding undifferentiated mass of paraxial mesoderm. There is no evidence of lids, conjunctiva, cornea, iris, ciliary muscles or processes or lacrimal apparatus. The embryo therefore represents the very beginning of ocular development.

SUMMARY

Serial sections and semidiagrammatic clay models of the eye of a 5.5 mm. embryo are described. Indications of the future development of the different parts are given. Reference is made to possible congenital abnormalities.

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PROBLEM OF RETINITIS IN THE DIABETIC PATIENT

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Diabetic retinitis is still an enigma not only to the ophthalmologist but to the internist as well. Too frequently is the internist confronted with a diabetic patient who has been referred by his conscientious "eye man" because of a retinitic state which, in fact, neither one can to any great extent influence. For the internist has come to realize that seldom does the most meticulous diabetic control of which he is capable cause any semblance of a reversal of the pathologic process in the eye or even a staying of the process. It would be well, therefore, if the two fields of medical endeavor would establish some mutual understanding as to their respective therapeutic limitations so that what little common knowledge is at hand might be used to the greatest advantage of the patient. What constitutes adequate diabetic control for the unfortunate patient, and what is the rationale of the prospective program?

It is universally accepted that diabetic retinitis is essentially a vascular disease practically synonymous with endarteritis, a part of the generalized arteriosclerotic process so common in diabetic patients who have had their disease for eight or more years. The age of the patient seems to have little bearing on the incidence of the retinitis. Waite and Beetham [1] have found the incidence to be related rather to the duration of the diabetes itself. Youth and the most adequate control with diet and insulin do not exempt diabetic patients from eligibility. It is therefore not surprising that the unbiased internist should consider present day therapy for diabetes seriously wanting in preventing the march of arteriosclerosis in general and of retinitis in particular. The high carbohydrate–low fat diets now in vogue have been thought to retard the speed of the process in that hyperlipemia is now far more rare than it was when the dietary trend was toward the high fat–low carbohydrate regimen. As a result, lipaemia retinalis in diabetic patients has now practically become a museum disease in its rarity. Until, however, the mechanism involved in the development of premature arteriosclerosis

Read before the Brooklyn Ophthalmological Society, by invitation, Oct. 16, 1941.

1. Waite, J. H., and Beetham, W. P.: New England J. Med. **212**:367 and 429, 1935.

in diabetic patients has been elucidated, there can be little hope of preventing or correcting retinitis.

The concept that fat economy in man is intimately bound up with the etiology of arteriosclerosis has recently been revived. Aschoff[2] championed the theory that lipoids are imbibed from the blood stream through the endothelium of the vessels and deposited in the intima preliminary to calcification of the involved areas. Anitschkow,[3] acknowledging such deposition of lipoids, including cholesterol, pointed to the fact that most commonly there is no clinical hypercholesteremia to be found even in the extremely arteriosclerotic patient. Certainly this is true of the well insulinized patient who is on a high carbohydrate–low fat regimen. An understanding of the body's preference for the utilization of carbohydrate[4] over that of fat explains in part the absence of hyperlipemia. Whenever it is at all possible the organism will metabolize carbohydrate and spare its own body fat, but especially is this true when the utilization of carbohydrate is encouraged by high ingestion of this moiety together with an adequate dosage of insulin. Normally carbohydrate metabolism is "explosive" in nature, whereas in the same person fat metabolism is rather sluggish. One need but observe a diabetic patient on a relatively high carbohydrate–low fat–low calory diet in order to satisfy oneself that the food economy is far more efficient then than when the patient is on a diet high in fat and relatively low in carbohydrate. For the same energy expenditure, the latter type of diet cannot possibly be kept isocaloric with the higher carbohydrate diet but must of necessity be 15 to 20 per cent higher in its caloric value. A. B. Macallum,[4] of Montreal, in a consideration of fat metabolism pointed out the fact that carbohydrate is normally a fat sparer far out of proportion to the relative caloric values of the two moieties. Thus 50 Gm. of dextrose (representing some 200 calories) in its oxidation will prevent or spare the mobilization and possible breakdown into its betahydroxystearic acid of 228.2 Gm. of tristearin. Since this amount of fat would in its combustion represent some 2,100 calories, and since this fat is mobilized but burned only in relatively small part for each possible deficiency of 50 Gm. of dextrose, the inefficiency of fat metabolism in general is plainly evident. For every deficit of the fat-sparing carbohydrate, tremendous amounts of fat must be mobilized from such fat depots as the skin. That this fat is not oxidized to its end products save in relatively small amounts is readily proved by calorimetry. A

2. Aschoff, L.: Med. Klin., Beihefte **4**:1, 1908; **10**:1, 1914.

3. Anitschkow, N., in Cowdry, E. V.: Arteriosclerosis, New York, The Macmillan Company, 1933.

4. Macallum, A. B.: Canad. M. A. J. **22**:3, 1930.

fair question would be: What happens to the mobilized fat which has not been used or which has not been lost through the urine as ketones? It must of necessity be redeposited somewhere in the body. Starvation (which is in truth a high fat diet of endogenous origin) is associated with tremendous deposition of neutral fat in the liver cells. The liver is known to be the chief, if not the only, site of oxidation of higher fatty acids down into their acetoacetic acids and ketones, which are in turn directly used by the body tissues much as is dextrose.[5] It is thought that some of this neutral fat which has been mobilized from the fat depots might be redeposited within the intima of blood vessels as easily as in the liver in the course of its passage from the original skin depots. There is a close analogy in diabetic patients between fat deposition in the liver and fat deposition in the vessel walls, for just as certainly as all patients with diabetes of a number of years' standing have atherosclerosis in varying degrees, so do all animals with diabetes of long standing have demonstrable fatty infiltration of the liver;[6] and there is no relationship whatever in either instance to the efficiency of the antidiabetic care previously exercised. The only depancreatized dogs which do not die with fatty infiltration of the liver are those fed raw pancreas in conjunction with their usual dietary and insulin care. In fact, it is well known that depancreatized animals under adequate dietary and insulin care alone die not of the diabetes per se but as a result of coincidental development of a fatty liver. Best[7] showed that choline administered to such animals will cause a reversal of the process of fatty infiltration of the liver or will entirely prevent its occurrence. He suggested that the choline content of the ingested raw pancreas may be responsible for this phenomenon. Dragstedt,[8] however, found that the same defatting effect could be accomplished by administering an alcoholic extract of the pancreas low in choline. This extract was termed lipocaic. It is thought that as the beta cells of the islands of Langerhans produce insulin, so the alpha cells of these islands elaborate a factor which prevents accumulation of fat in the liver or dissipates such fat

5. Stadie, W. C.: Ann. Int. Med. **15**:783, 1941.

6. Chaikoff, I. L., and Kaplan, A.: J. Biol. Chem. **106**:267, 1934. Kaplan, A., and Chaikoff, I. L.: ibid. **108**:201, 1935. Chaikoff, I. L., and Kaplan, A.: ibid. **112**: 155, 1935; Proc. Soc. Exper. Biol. & Med. **34**:413, 1936.

7. Best, C. H.: Ann. Int. Med. **7**:145, 1933. Best, C. H.; Ferguson, G. C., and Hershey, J. M.: J. Physiol. **79**:94, 1933. Hershey, J. M., and Soskin, S.: Am. J. Physiol. **98**:74, 1931. Best, C. H., and Ridout, J. H.: Choline as Dietary Factor, in Luck, J. M., and Smith, J. H. C.: Annual Review of Biochemistry, Stanford University, Calif., Annual Reviews, Inc., 1939, vol. 8, p. 349.

8. Dragstedt, L. R.: Present Status of Lipocaic, J. A. M. A. **114**:29 (Jan. 6) 1940.

once it has accumulated. It has been shown that this mechanism is active not only in dogs but in human beings. Figure 1 shows a photomicrograph of a section of liver taken at biopsy from a middle-aged woman with diabetes of long standing whose liver rather suddenly became enormous and who became unstable in respect to insulin control, changing from a state of hyperinsulinism to ketone coma within a few hours. A malignant process in the liver was suspected. At laparotomy this organ was found to be black with fat. It will be noted in figure 1 that the parenchymal cells are large and foamy and are so loaded with fat as to displace their nuclei and make tissue identification wholly dependent on the architectural arrangement of the cells themselves.

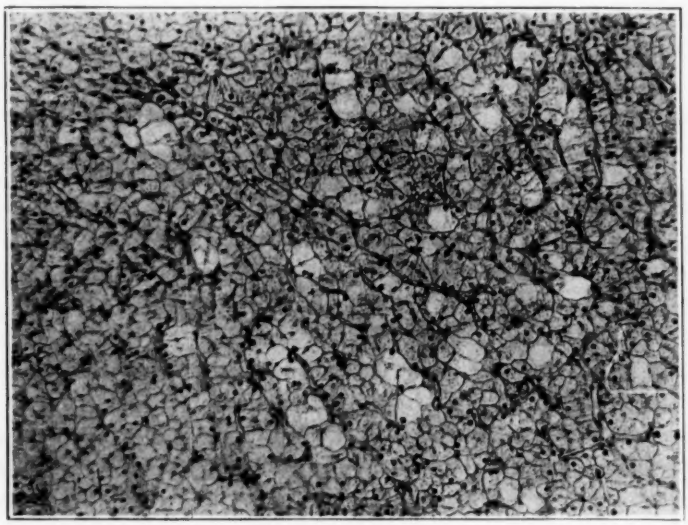

Fig. 1.—Section of liver showing such extreme fatty infiltration of the cells that the nuclei are displaced and tissue identification is difficult. The patient presented clinically a large liver and evidences of generalized arteriosclerosis without hyperlipemia.

The patient was fed raw pancreas, desiccated pancreas tablets and a high protein diet relatively high in carbohydrate and low in fat. With this regimen the liver was reduced to normal size within a few months. It is surprising that such accumulation of fat is not associated with detectable hyperlipemia. The values for cholesterol in the blood of this patient hovered about 78 mg. despite the enormous accumulation of fat in the liver. Moreover, it has been shown by earmarking subcutaneous fat that the fat present in the liver of experimental animals does not originate there but has been transported from such fat depots

as the skin.[9] It seems highly probable that the accumulated fat at some phase of its transportation made use of vascular channels in spite of the uniform finding of a low level of blood cholesterol and an absence of hyperlipemia. One must accept as possible the theory that such mobilization of fat from skin depots could in similar manner expose the arteries to the physical environment necessary for the imbibition of fat, as suggested by Aschoff. Dragstedt found that in his dogs deprived of the pancreas and not fed lipocaic there was a decided parallelism between the development of fat in the liver and of arteriosclerosis.[8] Since the dog is not prone to spontaneous arteriosclerosis, the coincidence of the two processes is certainly suggestive of the

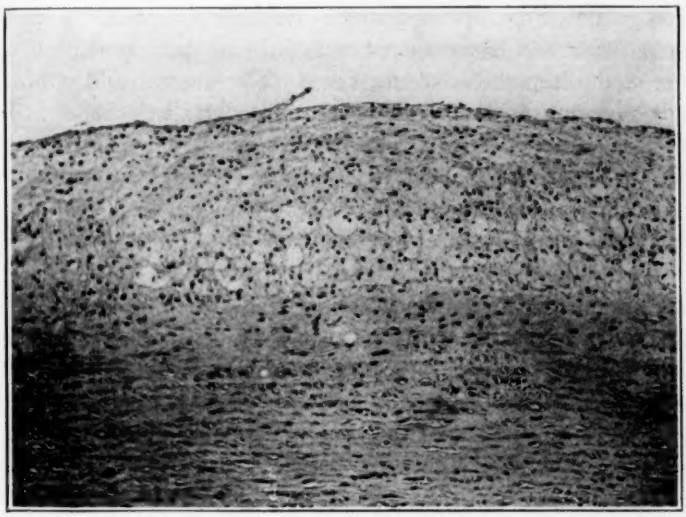

Fig. 2.—Section through an early atheromatous patch in the aorta showing thickening of the intima and foam cells filled with lipoid in proliferated intimal tissue.

presence of a common cause. Figure 2 shows an aortic arteriosclerotic lesion early in its development, with foam cells in the subintimal region not unlike those seen in the liver. It has been boldly asserted that the two processes may be one or at least kindred.

The analogy may be carried still further. When the liver of a diabetic patient becomes fatty, for some inadequately explained reason his carbohydrate tolerance seems to improve and his sensitivity to insulin increases. Hypoglycemia replaces hyperglycemia. The customary dose of insulin will throw him into insulin shock. Accordingly, improved

9. Macleod, J. J. R.: Physiology in Modern Medicine, St. Louis, C. V. Mosby Company, 1935, p. 702.

carbohydrate tolerance with the most complete insulin control does not mean or even suggest that the patient's liver has not already become fatty or is not in the process of doing so. In fact, dramatic improvement in utilization of carbohydrate and in sensitivity to insulin may be the first clinical suggestion that fatty infiltration of the liver has actually taken place. Similarly, it may fittingly be asserted that the subendothelial deposition of fat (preliminary to the calcification) associated with the arteriosclerotic process marches on in all diabetic patients whether or not they are under satisfactory dietary control.

There are in diabetic patients at least two mechanisms whereby a physical state or substratum is induced which favors the possibility of lipoid imbibition through the vessel walls. The first of these is the well recognized hyperlipemia which frequently occurs in untreated diabetic patients and is associated with ketosis, decreased carbohydrate tolerance and ultimately diabetic coma. The second and more subtle mechanism occurs in conventionally well controlled diabetic patients and is accompanied not by a detectable hyperlipemia but rather by an alipemic state, a low blood cholesterol content, increased insulin sensitivity and increased carbohydrate tolerance. This type of lipoid disturbance is possibly related to a deficiency of the secretion of the alpha cells of the islands of Langerhans, lipocaic.

Whether adequate administration of lipocaic will exert a beneficial effect in the prophylaxis of arteriosclerosis is at present unknown and is entirely out of the province of this paper. If, however, it is true that there is a direct relationship between arteriosclerosis and a faulty economy of fat, there rests on the shoulders of the internist an increased responsibility. For, although with his present knowledge he may not be able to prevent the ultimate development of arteriosclerosis, he may conceivably delay its evolution; certainly, by adequate use of the knowledge at hand he can often forestall some of the dreaded vascular accidents incidental to an already well developed arteriosclerosis. He can frequently prevent that most dreaded of accidents, retinal hemorrhage. Herein at present possibly lies his greatest opportunity. The rationale of his management will in general rest on three concepts:

First, there is need for the promotion of adequate carbohydrate metabolism in order to prevent fat mobilization. The Geelmuyden theory that "fat burns in the flame of carbohydrate" has been thoroughly disproved.[10] A. B. Macallum [4] has shown that fat is metabolized only when its utilization is made obligatory by a lack of adequate carbohydrate metabolism. The economy of such forced fat metabolism has, as already pointed out, been found to be most inefficient. Thus enormous

10. Chaikoff, I. L., and Soskin, S.: Am. J. Physiol. **87**:58, 1928. Friedemann, T. E.: J. Biol. Chem. **116**:133, 1936.

sclerosis and especially to diabetic retinitis is in order. There has never amounts of fat are of necessity mobilized from fat storage depots to cover what may be only a relatively small deficit in carbohydrate utilization. Ketones are created in excess of the body's ability immediately to use them, and some of these ketones are thus lost in the urine; but, more important, the tremendous excess of the mobilized fat is not all oxidized down to its ketones but is redeposited to disadvantage in the liver and possibly also in the blood vessels. The prevention of such fat mobilization should therefore be the clinician's aim. This can be accomplished by forcing carbohydrate utilization by means of a diet relatively high in carbohydrate and by the use of insulin. Insulin may be needed to prevent urinary loss of the ingested carbohydrate. Whereas the average diabetic patient commonly shows improvement in his carbohydrate tolerance only when the diet prescribed is mildly subcaloric,[11] the subcaloric approach should be scrupulously avoided in the arteriosclerotic diabetic patient lest even the mild caloric restriction result in undesirable fat mobilization to meet the deficit. Heretical as it may seem, reason would suggest that the obese diabetic patient with advanced arteriosclerosis should therefore not be subjected to weight reduction but should be kept in the status quo so far as his body weight is concerned. The appearance of ketones in the urine of such a patient would most certainly indicate that his caloric intake in the form of carbohydrate and/or protein was deficient and that endogenous fat was not being spared but was being actively mobilized. Similarly, excesses of exogenous or dietary fat must be avoided. Only the minimum of fat necessary for weight maintenance after a high carbohydrate diet has been prescribed should be allowed. This amount is usually in the neighborhood of 45 Gm. of fat daily.

Secondly, adequate or liberal protein should be prescribed. Goldschmidt [12] and Ravdin and others [13] have demonstrated the protective value of animal protein in the accumulation of fat in the liver and degeneration of the liver. Because Dragstedt [8] has shown a tendency to parallelism between a fatty liver and arteriosclerosis in dogs, it would seem rational to allow the arteriosclerotic patient a liberal intake of protein. In the diabetes clinic of the Brooklyn Hospital, the intake of protein of such patients is carried to between 85 and 150 Gm. daily.

Thirdly, the blood sugar should be kept at its optimal level. A critique of the so-called normal blood sugar level in relation to arterio-

11. Anderson, G. E.: Brooklyn Hosp. J. **2**:235, 1940.

12. Goldschmidt, S.; Ravdin, I. S., and Lucké, B.: J. Clin. Investigation **18**:277, 1939.

13. Ravdin, I. S.; Stengel, A., Jr., and Prushankin, M.: Control of Hypoproteinemia in Surgical Patients, J. A. M. A. **114**:107 (Jan. 13) 1940. Ravdin, I. S.: California & West. Med. **53**:68, 1940. Miller, L. L.; Ross, J. F., and Whipple, G. H.: Am. J. M. Sc. **200**:739, 1940.

been advanced any real experimental proof or even a suggestion that it is the high blood sugar level in diabetes that causes arteriosclerosis. Moreover, improvement in peripheral arterial disease (endarteritis) by the maintenance of the blood sugar at so-called normal levels for prolonged periods is conspicuous by its absence. While such an assertion means little for or against the possible role of a high blood sugar level in arteriosclerosis, the counterpart of a high level, a low level or a level kept below what is physiologic for the arteriosclerotic patient, has been shown to be most detrimental. The damaging effect of absolute or even of relative hypoglycemia in the arteriosclerotic diabetic patient has been so vividly impressed on students of diabetes that they often doubt the validity of accepted standards of normal for such patients and frequently keep the blood sugar of their patients at levels which in accordance with orthodox standards would be far too high. One must, however, bear in mind that such high levels in the arteriosclerotic diabetic patient must have as their premise an absence of glycosuria and an absence of weight change.

The nondiabetic arteriosclerotic patient often has a relatively high blood sugar level without urinary spill-over. He commonly has a high renal threshold for dextrose and therefore shows no urinary sugar despite a high blood sugar level. Careful studies of the respiratory quotient reveal that he utilizes ingested carbohydrate with normal facility. Accordingly, the purposeful reduction of the high blood sugar level in conformance with accepted standards would, as it were, be "gilding the lily," for once the so-called normal reading is established the patient is quickly transformed into a clinically sick man who is far more prone to vascular accident. Many clinicians agree that in the nondiabetic arteriosclerotic patient such treatment is far more destructive than would have been the original disease. Why should the diabetic patient with arteriosclerosis be subjected to the severe reduction in blood sugar which is so scrupulously avoided in the nondiabetic patient? May not the diabetic arteriosclerotic patient too be within his most physiologic limits when he has a high blood sugar level without glycosuria?

The rationalizing medical attendant readily appreciates the fact that in any diabetic person, arteriosclerotic or nonarteriosclerotic, ingested carbohydrate has only three possible paths available:

One, it may be lost to the organism, whereupon it will be found in the urine.

Two, it may be stored in the organism, whereupon it will be translated into an increment of body weight.

Three, if it is neither lost nor stored it must of necessity be used. Provided there is neither gain nor loss in weight nor glycosuria, it

makes no difference whether the organism uses dextrose from a high or from a low level in the blood. A high level may possibly be protective against the known danger of vascular accident in the arteriosclerotic patient deliberately kept at low levels. It would seem most unreasonable to keep the fragile arteriosclerotic diabetic patient within those so-called normal standards of blood sugar, which bear no more authenticity than a mere percentage of incidence.

But one must be certain that the high blood sugar of the arteriosclerotic diabetic patient is not accompanied by an increase in body weight. Such accretion would signify excessive storage of fuel or superalimentation, a state which would most certainly in the average diabetic patient jeopardize the carbohydrate tolerance. Of more immediate importance, however, than impaired tolerance is the well established fact that such superalimentation may promote hypertension, a dreaded state in the presence of fragile retinal vessels. By dietary adjustment alone an even balance between caloric intake and energy expenditure can usually be established and blood pressure often moderated thereby.

On the other hand, if with the high blood sugar there exists severe and persistent glycosuria, the resulting diuresis of important inorganic electrolytes (sodium, etc.) as well as vital amino acid nitrogen supervenes as a most undesirable complication. Electrolytic stabilization between tissues and fluids is thereby disturbed, a state being produced which some authorities consider to be the first step in the vascular injury usually preceding arterial degeneration. Moreover, such uncontrolled glycosuria will, much as does superalimentation, impair carbohydrate tolerance. Dietary restriction, however, as a corrective of the glycosuria must be most conservative lest a caloric deficiency call forth undesirable fat mobilization. Insulin, therefore, becomes the agent of choice under these conditions. Insulin is cautiously administered in increasing doses, stepladder fashion, so that the blood sugar will be brought to a point just below the threshold, or spilling over, level. The occasional accidental occurrence of temporary glycosuria (much in the nature of a brief alimentary glycosuria) requires no insulin provided, of course, there is complete recovery to the aglycosuric state before further ingestion of food.

With the foregoing premises in mind, one may consider what would constitute rational care of the elderly diabetic patient referred to the diabetes clinic in preparation for an operation for cataract. First of all, a diet is prescribed on the basis of caloric needs and to the end that the patient will neither gain nor lose weight (even though obesity is present). One will thus be assured that the unnecessary fat metabolism of a deficiency state or of superalimentation of fat will be averted. Constant vigilance over body weight and appropriate readjustment of

diet by trial and error will be called for. Usually a diet in the neighborhood of 25 calories per kilogram of normal body weight will be adequate for maintenance, provided, of course, the carbohydrate and the protein moiety are kept relatively high. If after a week of dietary measures alone, the glycosuria has not come under control, insulin is administered, but in the most conservative stepladder manner of increase. Determinations of the blood sugar are made periodically but especially after the aglycosuric state has been reached, so as to make certain that the blood sugar is kept not too low but somewhere near the threshold level for the patient. The level of blood sugar during fasting may, for example, be in the vicinity of 170 or 180 mg.; in the absorptive (after eating) periods, it may be 250 mg. or more. Provided glycosuria is absent, such levels are probably most desirable in the arteriosclerotic diabetic patient and more physiologic than 120 and 170 mg., respectively. It is recognized that the liver glycogenizes much more effectively when the blood sugar is in the higher levels, thereby tending to improve the patient as a surgical risk. Whereas the lower blood sugar readings might for the average diabetic patient be entirely physiologic, for the arteriosclerotic patient they would indicate a relative hypoglycemic state and would call forth a compensatory suprarenal response [14] and a resulting tendency to hypertension. It is possible that some of the hemorrhages in the retina and into the anterior chamber which occur after operation result from postoperative hypoglycemia. It is precisely this accident which has prompted experienced ophthalmic surgeons to omit most scrupulously the last dose of insulin preliminary to cataract extraction. An appreciation of the hazards of hypoglycemia both relative and absolute should forestall heroic and meddlesome attempts to lower the blood sugar.

Wagener,[15] of the Mayo Clinic, has expressed the thought that some factor in the diabetic patient other than the disturbance in carbohydrate metabolism is responsible for the premature retinitis which occurs. He, too, suggests that the process is in some manner linked with fat metabolism. According to his experience, the condition develops somewhat more slowly with a high carbohydrate–low fat regimen than with the reverse, but even with the most careful sugar control retinitis may make its appearance. The basis of the retinitis seems to be vascular. Accordingly, it is not surprising that Waite and Beetham [1] found retinitis in 59 per cent of their patients who had had diabetes for more than fifteen

14. References listed by Davis, B. L., and Van Winkle, W.: J. Biol. Chem. **104**: 207, 1934.

15. Wagener, H. P.: Ocular Complications of Diabetes Mellitus, in Fundamental Concepts in the Treatment of Diabetes Mellitus and Its Complications, New York, The New York Diabetes Association, 1941-1942, nos. 19 and 20.

years. In fact, this estimate would seem rather conservative, since arteriosclerosis itself is found in practically 100 per cent of patients who have suffered from diabetes for even eight years.

In conclusion, in the present state of knowledge what can one hope to accomplish (1) for the patient who is likely to acquire diabetic retinitis and (2) for the patient who already has such retinitis?

First: Treat diabetic patients early in their diabetes with diets relatively high in carbohydrate, low in fat and low in calories, together with adequate insulin if needed, so that long before arteriosclerosis has developed excessive stores of fat in the body have been reduced to a minimum. This measure will prevent that type of hyperlipemia which is so commonly present in the untreated or poorly treated diabetic patient. It will not prevent the eventual development of the fatty liver of lipocaic deficiency which is by some investigators thought to go hand in hand with the evolution of arteriosclerosis. It is conceivable, however, that the arteriosclerosis and its retinitis may possibly be delayed by adequate diabetic control with a diet high in carbohydrate, high in protein and low in fat but adequate in calories. Only by some measure other than these and possibly in the nature of the administration of lipocaic is it likely that prevention will finally be accomplished.

Secondly: When arteriosclerosis and its sequel, retinitis, have actually developed, the internist's aim in treatment should be to avoid those physical states which favor a more rapid evolution of the process. In addition, efforts should be made to prevent needless vascular accidents in already damaged vessels. The process may be partially stayed by scrupulously preventing unnecessary fat mobilization and inefficient fat metabolism by keeping the diet adequate in carbohydrate and calories to maintain body weight. The withholding of all but a minimum intake of fat (about 45 Gm.) is also a factor in diverting the patient from unnecessary fat metabolism, as is a relatively high carbohydrate (250 to 300 Gm.) and protein (85 to 150 Gm.) content. Loss of weight or ketonuria is a sure indication that the body is not sparing fat but is being driven to a most undesirable metabolism of the endogenous fat. The second desideratum, the avoidance of vascular accidents, can in part be accomplished by the clinician's acquiring a respect for the patient's physiologic blood sugar level, guarding against heroic reductions in blood sugar, avoiding meddlesome tampering and moderating the blood sugar level only when it is associated with a gain in weight or persistent glycosuria or both.

The present defeatism of the internist has resulted from his inability materially to modify by means of conservative antidiabetic treatment arteriosclerosis in general or retinitis in particular. He is obliged to

use to the best, if not completely satisfactory, advantage what little knowledge is at hand and to look hopefully for future discoveries. The clinician awaits with eagerness adequate experimental appraisal of lipocaic as a means of preventing the most dreaded of diabetic complications, arteriosclerosis. In the meantime, the ophthalmologist should bear patiently with the shortcomings of the internist, for it will be his envied lot to see firsthand in the retina any improvement which the internist may in the future be able to accomplish.

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RETINAL BLOOD PRESSURE

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The various disease processes which produce retinal vascular fundus disease are usually of a progressive nature. In most of these conditions the changes in the vessels occur slowly and little is known of the true mechanisms attending them. Some authors believe that the most important pathologic variations occur within the capillary bed, and in the case of hypertension, retinal hemorrhages and edema follow capillary decompensation. According to this concept it is extremely important to investigate the blood pressure of the retinal vessels and correlate changes in caliber with changes in pressure. At the present time only one clinical method has been recommended for the determinations. This method is called tonoscopy or ophthalmodynamometry. It is the purpose of this paper to discuss its application to the study of retinal vascular fundus disease.

TONOSCOPY

It has long been known that compression of the eyeball produces pulsations in the retinal vessels. Magitot [1] and others have shown that the arterial pulsations occur when the intraocular tension is equal to the diastolic pressure of the central artery of the retina. These pulsations disappear, and later the arteries begin to collapse when the intraocular tension is made equal to and then exceeds the systolic blood pressure in the central retinal artery.

In 1909 Bailliart [2] and later Black [3] and Deyl observed that it required more pressure on the globe to overcome these pulsations in hypertensive patients. Henderson,[4] working on a clinical method for estimating the arterial diastolic pressure in the eye, devised a small pressure gage for recording the pressure required to initiate venous compression. Little use was made of this method until Bailliart [5] in 1917 suggested an improved technic for recording the readings and drew up a chart for

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1. Magitot, A. P.: Am. J. Ophth. **8**:777, 1922.
2. Bailliart, P.: Clin. opht. **15**:178, 1909.
3. Black, M.: An Index to the General Blood-Pressure, J. A. M. A. **57**:362 (July 29) 1911.
4. Henderson, T.: Tr. Ophth. Soc. U. Kingdom **34**:309, 1914.
5. Bailliart, P.: Ann. d'ocul. **154**:257, 1917.

interpolating pressures. The figures in this chart were determined by animal experimentation, and lines were plotted to denote the alteration in intraocular tension when measured pressure was applied horizontally to the cornea. The initial tensions varied from 10 to 50 mm. of mercury.

The investigations of Bailliart together with those of Magitot added considerable impetus to the work, and various other instruments have since been devised. The most important of these are the ones described by Uyemura and Suganuma,[6] Sobanski,[7] Keil [8] and Kukan.[9] All these save that described by Kukan are modifications of Bailliart's instrument. Kukan's instrument is an ingenious device consisting of a negative pressure system involving a manometer, sucking disk and suction pump. According to the relationship expressed by Kukan, positive pressure can be applied to the eyeball when the sucking cup is held in apposition to the globe and negative pressure applied. He has shown mathematically that the pressure which sucks the cup simultaneously delivers pressure to the rim of the cup. When the surface area of the sucking portion exceeds that of the rim, compression occurs and the intraocular tension rises. The sucking cups vary in diameter from 11 to 13 mm. Thus there is a maximum reading of approximately 85 to 105 mm. of mercury, respectively, depending on the level of the intraocular tension.

To evaluate the findings determined by tonoscopy it is necessary to recall, first, that the arterial pressure in the retinal arteries is higher than the intraocular tension; second, that the venous pressure may be less or equal to or exceed the intraocular tension, and, third, that the capillary pressure ranges between that of the arterial and that of the venous pressure.

To produce pulsations in the arteries or veins at the disk, the intraocular tension must exert a force on the vessel walls equal to the pressure in the blood column during diastole. According to Magitot, three changes may be observed in the artery during the course of progressive ocular compression. When the intraocular tension begins to equalize the diastolic arterial pressure, a tremor occurs in the vessel. This is followed by a steady beat, which he attributed to the average pressure, and the point at which pulsations occur before complete collapse denotes the systolic pressure. Magitot stated the belief that the average diastolic pressure is the most important and the systolic, which is often hard to elicit, relatively unimportant. In the healthy adult, according to Bailliart,[10] the

6. Uyemura, M., and Suganuma, L.: Acta ophth. soc. jap. **38**:1835, 1934; Klin. Monatsbl. f. Augenh. **96**:481, 1936.

7. Sobanski, J.: Klin. Monatsbl. f. Augenh. **96**:351, 1936.

8. Keil, J.: Klin. Monatsbl. f. Augenh. **99**:625, 1937.

9. Kukan, F.: Ztschr. f. Augenh. **90**:166, 1936.

10. Bailliart, P.: The Retinal Circulation, translated by J. Lebensohn, Chicago, The Professional Press, Inc., 1928.

average diastolic arterial pressure is about 35 to 40 mm. of mercury, or approximately 50 per cent of the diastolic brachial pressure, and the average retinal systolic pressure about 70 mm. of mercury. The reading must be made rapidly to avoid a reflex increase in blood pressure.

Tonoscopy of the veins is far more complex. The pulse or rhythmic venous collapse, which may be present or elicited, occurs during arterial systole and the vein refills during arterial diastole. The venous pulse, unlike the arterial, is complex and composed of a multitude of capillary impulses. Normally it assumes two forms (Fritz [11]). In the first it appears as a rapid flattening of the vein with few if any pulsations. This is often hard to recognize especially when the flattening is slight. In the second, which occurs more frequently, the vein shows a flattening with pulsations of equal amplitude, beginning at the onset of the venous collapse and terminating with increased ocular compression. So far as the elicitation of the venous pulse is concerned, Bailliart [10] divided normal patients into three groups:

1. Those with spontaneous venous pulse. This occurs when the intraocular tension is increased sufficiently during systole to produce a partial collapse of the vein and the vein dilates again during auricular systole and ventricular diastole.

2. Those with venous pressure greater than the intraocular pressure. So long as the venous pressure exceeds the intraocular pressure no spontaneous pulse occurs. Under these conditions it is possible to elicit a venous pulse by increasing the intraocular tension through ocular compression.

3. Those with a venous pressure less than the intraocular pressure. When the intraocular pressure exceeds the venous pressure no venous pulse can be elicited until the venous pressure is elevated by jugular compression or by lowering of the intraocular pressure.

Concerning the retinal capillary pressure no direct clinical data are available. Fritz,[11] however, has approached the problem in an interesting manner. He stated the belief that retinal capillary studies must be made at the level of the larger veins which the capillaries contact. This is logical, since the venous flow is the sum of many capillary impulses and the characteristics of capillary homogeneity and heterogeneity are demonstrated by its simplicity or complexity. Thus, when the capillary flow is in a normal state of equilibrium (isoperfusion) the venous pulse, elicited by ocular compression, will remain of equal amplitude whether it has a rapid flattening without pulsations or a flattening accompanied by pulsations. On the contrary, in heterogeneous capillary circulation there exists in the vein into which the capillaries open a complex pulse. This pulse usually maintains one or the other of the two types previously

11. Fritz, A.: Tr. Internat. Ophth. Cong. (1937) **2**:218, 1938.

mentioned, but on this are grafted the remnants of heterogeneity, which serve to differentiate it from the homogeneous form.

The heterogeneity falls into three main classes:

1. The majority of capillaries are uniformly irrigated, except for a few constricted capillaries under weaker pressure. Under the influence of increasing ocular compression, small pulsations or slight flattening appears before those which characterize isoperfusion.

2. The majority of capillaries are irrigated uniformly, except for a few dilated under greater pressure. The heterogeneity is indicated by the delayed flattening and prolonged small pulsations observed toward the end.

3. Besides the majority of capillaries uniformly irrigated, others are perfused under weaker and stronger pressure. This gives a combination of 1 and 2.

Fritz's work suggests the possibility of perfecting a technic for identifying the heterogeneous capillary circulation, the degree of differentiation to be determined by the level of the ocular compression at which these classes of heterogeneity appear as compared with the level of the principal group. From a practical standpoint the determination is difficult, as few patients can be accurately grouped or the degree of differentiation determined. These difficulties suggest that the problem must be approached at least in part from the physical side and investigated according to the laws which control the passage of liquids through a tubular system contained within a closed space.

PRINCIPLES GOVERNING THE PASSAGE OF FLUID THROUGH TUBULAR SYSTEMS

The most extensive studies on the passage of fluid through tubular systems were made by Priestley Smith [12] in 1917-1918. His observations are so comprehensive that no additional work should be attempted without a preliminary review of the principles which he set forth in his scholarly communications. In a series of experiments he arranged single and branching tubes which were comparable to a simplified retinal circulation, and by placing manometers at various points throughout the system he studied changes produced by altering the aggregate cross section of the branches.

The data obtained enabled Priestley Smith to formulate principles governing the passage of fluid through tubular systems and to express certain of the relationships mathematically. For the purpose of this paper the following two principles are of extreme importance:

1. The fall in pressure in a tubular system is directly proportional to the resistance.

12. Smith, P.: Brit. J. Ophth. **1**:657, 1917; **2**:257, 1918.

2. To find the relative resistance in different regions of a tubular system in which companion branches are of equal size, square the total cross section in each region and divide by the number of branches in that region; the products are inversely proportional to the resistance.

These mathematical relationships can be more easily understood by an examination of figure 1. Two values shown in this illustration are known: *A* equals 104 mm. of mercury, the systolic pressure at the optic disk, and *B* equals 24 mm. of mercury, the venous pressure at the optic disk. The difference between *A* and *B* equals the total fall in pressure, or 80 mm. of mercury. Now if the cross sections are to each other as the square of the diameters, and resistance inversely proportional to the square of the cross sections, the resistance in vessels of 3 : 4 arterio-

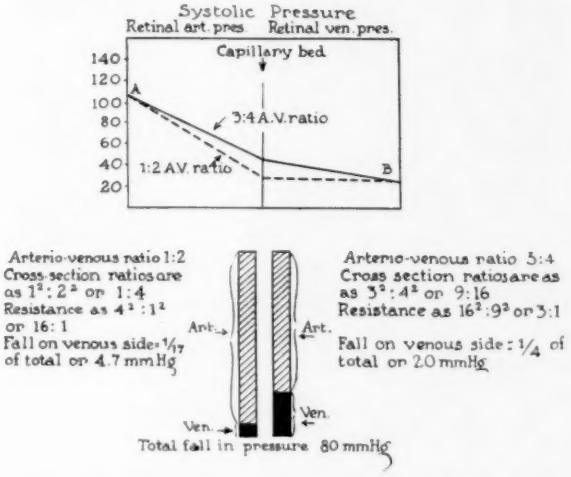

Fig. 1.—Capillary bed pressure and its relationship to the arteriovenous ratio.

venous ratio is as 3 : 1. Since the fall in pressure is directly proportional to the resistance and the total fall is 80 mm. of mercury, the fall on the arterial side equals 60 mm. and the venous fall equals 20 mm. of mercury. It follows that if the arteriovenous ratio is as 3 : 4 the systolic pressure in the capillary bed equals approximately 24 plus 20, or 44 mm. of mercury. By a similar process of reasoning and mathematics a 1 : 2 arteriovenous ratio produces only one seventeenth of the total fall on the venous side, or a capillary bed pressure of 28.7 mm. of mercury.

These figures show that the pressure in the capillary bed can be made to fluctuate by alterations in the arteriovenous ratio. Likewise, it can be shown that diffuse angiospasm and capillary constriction would result in an elevation in arterial tension. Such reactions would

seem to be well within the scope of reflex behavior and constitute a mechanism for maintaining equilibrium. The true nature of such reactions is difficult to determine, but to do so presents one experimental approach to the study of retinal vascular fundus disease. The problem resolves itself into one of calibrating the retinal blood vessels, determining the retinal arterial and venous pressures and plotting the pressure curves according to Priestly Smith's principles.

EXPERIMENTAL STUDIES

Twenty-five medical students were selected during the course of refractions with homatropine-paredrine cycloplegia and their fundi photographed according to a method previously described.[13] Kukan's ophthalmodynamometer in combination with a Bausch and Lomb mercury vapor arc binocular ophthalmoscope was then used to determine the retinal arterial diastolic and venous pressures (fig. 2). The average arteriovenous ratio was found to be as 3:4 and was calculated by projecting the positive transparency on a screen and measuring comparable diameters of the artery and of the vein. Figure 3 shows a typical normal fundus with individual curves for the retinal systolic and diastolic pressures. *A* and *B* represent the diastolic arterial and venous pressures, respectively; *C* was derived according to Bailliart's formula.

Comparable studies were made on 40 patients with cardiovascular-renal disease. These patients were divided into groups according to the convenient classification recently described by Gifford and Macpherson,[14] as follows:

Group 1. Retinal arteriosclerosis
Group 2. Retinal arteriosclerosis with retinopathy
Group 3. Diffuse retinal arteriolar constriction
Group 4. Diffuse retinal arteriolar constriction with retinopathy (hypertensive retinopathy)
Group 5. Diffuse retinal arteriolar constriction with neuroretinopathy (hypertensive neuroretinopathy)

Groups 1 and 2 separate cases of localized vascular changes associated with benign hypertension from those in which there is diffuse angiospasm (groups 3, 4 and 5). As Gifford and Macpherson have pointed out, it is often impossible to classify hypertension as to the varying grades of severity. Likewise, it is impossible to separate the

13. Puntenney, I.: Am. J. Ophth. **23**:1113, 1940.

14. Gifford, S. R., and Macpherson, W. A.: Quart. Bull. Northwestern Univ. M. School **14**:65, 1940.

two types completely, and it is much simpler to divide the cases into groups rather than grades, as suggested by Wagener and Keith.[15]

This grouping and clinical study can be more easily understood through examining the fundus pictures and pressure curves in figures 3 and 4. Each group is represented by the individual findings in a

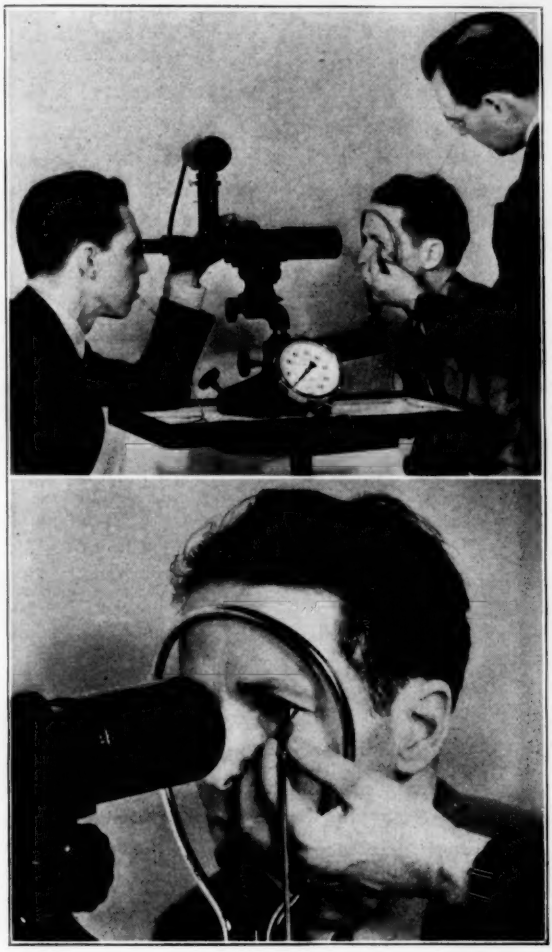

Fig. 2.—Binocular ophthalmoscope in use with the Kukan ophthalmodynamometer.

fairly typical case. The readings must not be interpreted as average readings derived from the total patients studied in each group, because it is difficult to compile such data accurately. The pressure curves

15. Wagener, H. P., and Keith, N. M.: Am. J. M. Sc. **197**:332, 1939.

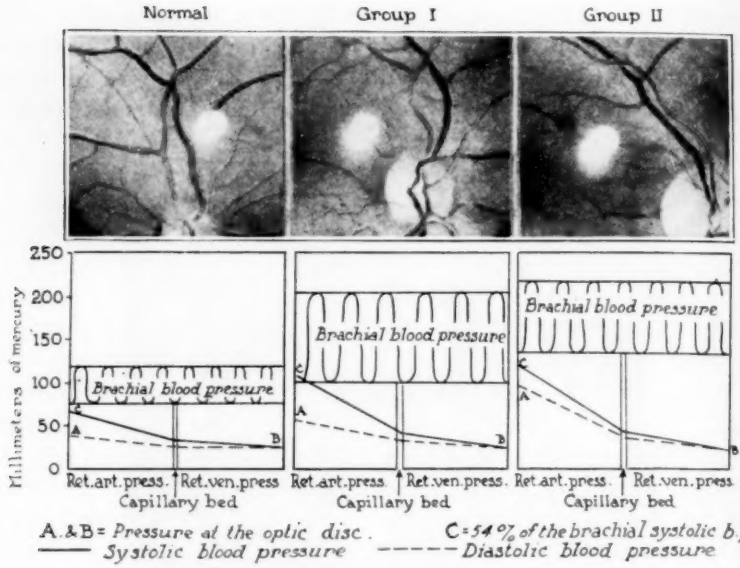

Fig. 3.—Retinal arterial, venous and capillary pressure in normal persons and in groups I and II.

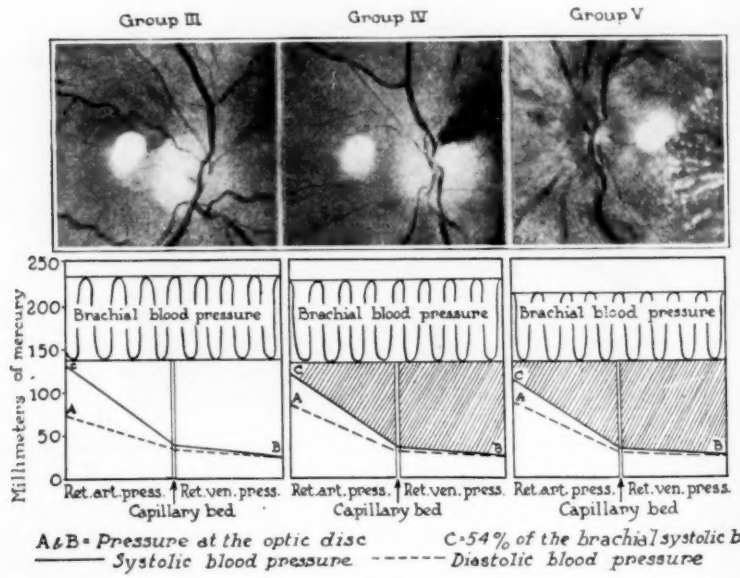

Fig. 4.—Retinal arterial, venous and capillary pressure in groups III, IV and V.

for the normal patients and groups 1 and 2 (fig. 3) were plotted from the individual readings shown in the accompanying table. A comparison of the retinal and the brachial pressure of the patients selected to represent the two groups shows the pressure to have been higher in group 2 (table). This is often the case, but no arbitrary figure can be selected as marking the level at which retinopathy will occur.

Similar fundus pictures and curves are shown in figure 4. The patients represented, who were selected to illustrate groups 3, 4 and 5, showed diffuse arteriolar constriction with an arteriovenous ratio of approximately 33:100 to 50:100. The brachial blood pressure curves show the diastolic pressure to have been about the same in all groups, but the retinal diastolic was the lowest in group 3. The capillary bed pressure shown in the systolic and the diastolic pressure curves was calculated according to Priestley Smith's principles. The fluctuation

Readings for the Individual Patients Selected in the Hypertensive Series

Classification	Brachial Blood Pressure	*A* Retinal Arterial Diastolic Pressure, Mm. of Mercury	*B* Retinal Venous Pressure, Mm. of Mercury	*C* Retinal Arterial Systolic Pressure, Mm. of Mercury	Retinal Arteriovenous Ratio	Retinal Capillary Pressure, Systolic-Diastolic Range	Theoretic Capillary Pressure with 3:4 Ratio
Normal	120/ 78	34	23	65	75:100	26-33	.....
Group I	205/105	60	22	110	70:100	29-39	.....
Group II	220/132	85	22	119	70:100	35-41	.....
Group III	230/134	75	23	125	33:100	26-27	36-48
Group IV	225/133	85+	28-85	121	33:100	21-32+*	42-52
Group V	210/132	85+	26-85	113	50:100 (varied)	29-32+*	41-48

* See shaded areas, figure 4.

in pressure computed on a 1:3 ratio equaled approximately 1 mm. of mercury. A third value for systolic capillary pressure, based on a 3:4 ratio, is shown in the table. This is a theoretic representation of the capillary pressure based on a normal arteriovenous ratio without a shift in the given pressures.

The venous pulse as elicited in the individual patients of groups 4 and 5 was of the heterogeneous type with impulses of unequal magnitude persisting to the level of the diastolic arterial retinal pressure. The pulsations of the main group occurred at the level shown by *B* (fig. 4). The high pressure present in an unknown percentage of the capillaries and the precapillary and the postcapillary arterioles and venules has been shown by a shaded area. This shaded area represents a zone of increased pressure in which the capillaries and the end vessels are thought by some investigators to be in the various stages of decompensation.

In a large number of other patients presenting almost the same picture of vascular fundus disease the venous pressure could not be elicited even after jugular compression. In many of these patients the diastolic retinal pressure was too high to be measured, and some were too ill to be photographed easily.

COMMENT

The relationship between changes in caliber and fluctuations in pressure in the retinal arterioles and capillaries is of fundamental importance to the study of hypertension. The importance can be appreciated when an attempt is made to differentiate the several forms of retinal vascular fundus disease and correlate the retinal findings with data secured by the internist. From the research and the objective point of view the ophthalmologist must study the hypertensive fundus from the standpoint of the theories of two schools of thought. The first theory is based on the assumption that the changes in the retinal vessels are compensatory in nature and secondary to the hypertension. The second, which is the more commonly accepted one, ascribes the changes in the retinal vessels to the primary cause of the disease. Since conclusive proof is lacking in the confirmation of the latter theory, it is worth while to examine this study from both points of view.

The capillaries are structurally the most delicate part of the whole retinal vascular system. Like the capillaries found elsewhere in the body, they are capable of response to direct stimulation and to vascular reflexes. The reactions are all so complex that little is known concerning their obscure mechanisms, but it is known that under normal conditions an equilibrium is maintained in the retinal circulation. This equilibrium depends on the delicate adjustment between intraocular pressure, arterial tension, capillary pressure and venous pressure.

It has been demonstrated [16] that the retinal arterioles show little change in their caliber when the retinal circulation is suddenly confronted with an increase in arterial pressure. The veins, however, usually become enlarged. The enlargement is believed to be the result of a passive dilatation following an increased flow through the capillary bed. The reserve capillaries, which are brought into use, serve as physiologic safety valves, and the increased blood flow is followed by a drop in pressure. When the retinal circulation is confronted with a prolonged elevation in arterial tension, more complicated adjustments are needed for the maintenance of equilibrium. What are some of the compensatory reactions? The first, which has been previously mentioned, is a dilatation of the capillary bed. If this occurs locally the venous pressure will rise. The pressure curves in figures 3 and 4 show

16. Puntenney, I.: Effect of Certain Chemical Stimuli on Caliber of Retinal Blood Vessels, Arch. Ophth. **21**:581 (April) 1939.

that the retinal venous pressure does not become elevated in hypertension until the retinal circulation becomes decompensated; consequently a prolonged rise in venous pressure is to be avoided. If the venous pressure is to remain at a fairly constant level the variables in the retinal circulation become limited to those which are capable of producing a fall in pressure by increasing the resistance in the vessels which lead to the veins. There are two mechanisms for accomplishing this result. The first is a narrowing of the vessels in the capillary bed. This lowers the pressure before the blood reaches the veins. The second is a reduction in the size of the lumens of the retinal arterioles. The latter may be accomplished by a gradual thickening of the vessel walls or by a contracture of whole vessels, commonly known as angiospasm.

If a fall in pressure is brought about by an increased resistance, what proportion of this resistance is shared by the capillaries and the arterioles? According to Priestley Smith's principles, the caliber of the arterioles offers the most reliable answer to the question. When the arteriovenous ratio remains fairly normal the capillaries bear the brunt of reducing the pressure. This can be tolerated fairly well as long as the retinal systolic and diastolic pressures are not too high. When the arterioles show a reduction in caliber the resistance is more evenly distributed.

Since the reactions in an equilibrium are reversible, the same retinal vessel finding as occurs in primary hypertension can occur when the hypertension is secondary to an increased resistance in the capillaries and arterioles. This is simply a reversal of the sequence between changes in caliber and hypertension, and the reactions are so closely integrated that this aspect of the problem is entirely dependent on the causation of the hypertension.

The Priestley Smith curves which have been used in this study are of course not accurate pressure curves. The truth of this statement becomes apparent when it is recalled that the variables in the capillary bed have been ignored. The curves do show, however, that the capillary pressure fluctuates over a rather narrow range as compared with the great variations in systolic and in diastolic arterial pressure. This narrow range is more easily maintained when the arterioles show an increased resistance. In many patients, however, the reduction in caliber of the arterioles is not proportional to the height of the arterial pressure. This means that the capillaries are responsible for the maintenance of the increased resistance and a relatively constant venous pressure. How do the capillaries accomplish this end? Do some of them contract and thus increase the resistance, or is the whole capillary bed in a state of semicontraction? From a physiologic standpoint, only a small number of capillaries are normally permeable to the blood stream, and the rest, which are momentarily at rest, remain impermeable. From this fact it follows that if an increased number of capillaries

become permeable, but in a state of semicontraction, the total resistance in the capillaries will be increased but the pressure in the individual capillaries will not be markedly altered. This compensatory mechanism is adequate as long as some of the capillaries can be held in reserve. When a reserve is no longer possible, many of the capillaries lose their contractility and dilate, and this change is followed by extensive edema and hemorrhage. The picture of capillary decompensation, existing in the various stages from isolated flame-shaped hemorrhages to severe neuroretinopathy, is indicative of the variability of capillaropathy.

It may be argued by some investigators that the maintenance of a normal venous pressure is a function of the heart rather than of the arterioles and capillaries and, furthermore, that an increased systemic venous pressure seldom occurs until the heart begins to show decompensation. These arguments are valid as they apply to the general venous pressure but not as they apply to the retinal venous pressure. The retinal veins are a portion of the lesser circulation. Since they are located far from the heart and close to the capillary bed, the elicited venous pulse frequently shows peculiarities which are thought to be caused by changes in pressure in the arterioles and capillaries and indicative of beginning capillary decompensation. In some patients small impulses of diminishing intensity persist to the level of the retinal diastolic pressure. They can be interpreted as the result of a dilatation of some of the capillaries with an associated increase in venous pressure. The shaded areas for groups IV and V illustrate these findings. However, in a large number of other patients presenting almost the same picture of vascular fundus disease, the venous pulse could not be elicited even after jugular compression. This, of course, suggests a high venous pressure, but such a conclusion is incompatible with previous findings. The only adequate explanation seems to be that the pressure applied by the instrument produced a temporary rise in venous pressure. This may be of some diagnostic importance, but it is more logical to believe that it is indicative of the limitations of ophthalmodynamometry.

These observations raise the question of the practical clinical value of determinations of the retinal blood pressure. The experience gained in the present study is of some value in clarifying this question. An examination of the diastolic pressure readings for all the patients studied in the five groups offers the following significant findings:

1. There is no particular pressure level at which retinopathies make their appearance.

2. No classification can be based on the readings. This conclusion agrees with the recent work of Koch.[17]

17. Koch, F. L. P.: Retina in Systemic Vascular Hypertension: Clinical Study of Caliber of Retinal Arterioles and Retinal Arterial Diastolic Blood Pressure, Arch. Ophth. **26**:565 (Oct.) 1941.

3. Many patients show pressures too high to be recorded with the Kukan instrument.

4. Clinical improvement is not always followed by a lowering of the pressure.

Likewise:

1. The venous pressure remains within normal limits until decompensation occurs.

2. Decompensation is often associated with a change in the character of the elicited venous pulse.

3. The venous pulse cannot be elicited in many patients with high retinal arterial pressure.

These observations, although by no means conclusive, show that many of the findings are still open to interpretation, and this fact limits the usefulness of the ophthalmodynamometer to research work. Thus its value as a clinical instrument in the treatment of the hypertensive patient and in determination of the prognosis cannot be established until a carefully conducted series of case studies have been made and the compiled data correlated with the course of the disease. Such studies are now in progress at Northwestern University Medical School, and the results will be reported when the work is completed.

SUMMARY

1. The history of the ophthalmodynamometer is discussed together with its use in determining the retinal arterial, venous and capillary pressure.

2. Principles governing the passage of fluid through tubular systems are cited.

3. Photographic studies are presented, together with graphs, showing the arterial venous and capillary pressures in hypertensive patients grouped according to the classification of Gifford and Macpherson.

4. The relationship between changes in caliber and fluctuations in pressure in the retinal arterioles and capillaries is described.

5. Changes in the venous pressure are correlated with capillary decompensation.

6. The limitations of ophthalmodynamometry are discussed.

Dr. Sanford R. Gifford provided advice and criticism, and Dr. M. Herbert Barker made possible the study of a large number of hypertensive patients.

303 East Chicago Avenue.

FOSTER KENNEDY SYNDROME ASSOCIATED WITH NON-NEOPLASTIC INTRACRANIAL CONDITIONS

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AND
N. S. SCHLEZINGER, M.D.
PHILADELPHIA

Leslie Paton [1] in 1909 was the first to call attention to the observation that in association with a basofrontal tumor there is apt to be atrophy of the optic nerve on the side of the tumor and choked disk on the opposite side. However, it was Foster Kennedy,[2] in 1911, who emphasized and amplified this ophthalmologic symptom complex, which he felt was diagnostic of the presence of a basofrontal tumor or abscess. According to him the symptom complex comprised the existence of a central scotoma and primary optic nerve atrophy in the eye on the side of the lesion with concomitant papilledema in the opposite eye. Since that time this syndrome has been included in practically all the standard textbooks on neurology and has come to be recognized, when present, as a diagnostic criterion of the existence of an expanding lesion of the basofrontal region or the anterior fossa. Recently, we have been concerned with 2 patients who presented the essential features of the Foster Kennedy syndrome. An intracranial expanding lesion was suspected in both of these patients. This original diagnostic impression, based largely on the existence of a Foster Kennedy syndrome, was not substantiated in either. They demonstrate that this syndrome in certain instances may be the result of a non-neoplastic intracranial disorder. From a neuro-ophthalmologic standpoint, this fact deserves emphasis.

REPORT OF CASES

CASE 1.—*History.*—W. B., a man aged 61 years, was admitted to the Wills Hospital on Jan. 15, 1940 with the complaint of blurred vision in the left eye of one week's duration. One year prior to admission frontal headaches had developed. At that time his physician informed him that he had arterial hypertension. Subsequently the patient noted some unsteadiness in walking. One month before he

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1. Paton, L.: A Clinical Study of Optic Neuritis in Its Relationship to Intracranial Tumors, Brain **32**:68, 1909.

2. Kennedy, F.: Retrobulbar Neuritis as an Exact Diagnostic Sign of Certain Tumors and Abscesses in the Frontal Lobes, Am. J. M. Sc. **141**:355, 1911.

entered the hospital he fell, and after this accident he noticed blurred vision in the left eye. The headache and blurred vision persisted. Because of the history of headache and the discovery of a Foster Kennedy syndrome the suspicion of a subfrontal neoplasm was entertained and the patient was transferred to the neurologic service at the Jefferson Medical College Hospital, on January 23.

Examination.—The patient was a well developed man who appeared older than his chronologic age. Marked generalized arteriosclerosis of the palpable peripheral vessels was present. The heart was moderately enlarged. The blood pressure was 190 systolic and 110 diastolic. The patient was alert and well oriented. Olfaction was preserved, but some examiners felt that it was relatively diminished on the right side. The left pupil was larger than the right, but both pupils reacted well to light and in accommodation. Fundus examination revealed pallor of the right optic disk and 2 D. of papilledema of the left optic disk. Retinal arteriosclerosis was present bilaterally. There was a suggestive weakness of the right-hand grip. The remainder of the neurologic examination gave negative results.

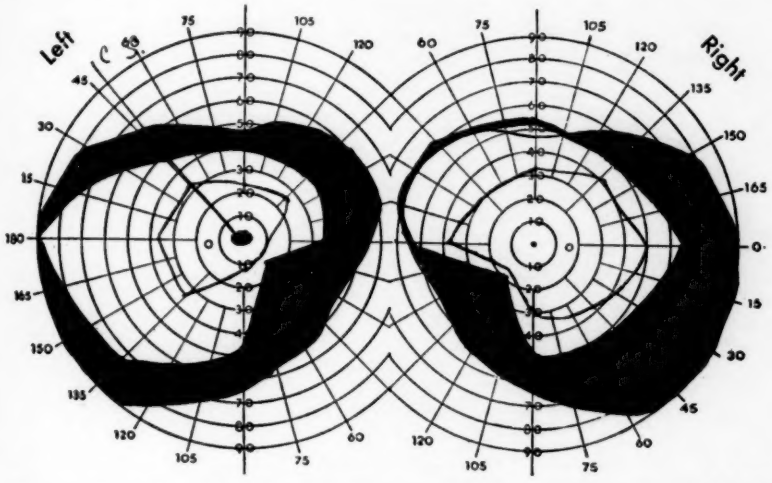

Fig. 1 (case 1).—The visual fields on admission, showing binasal inferior quadrantanopsia and a central scotoma on the left.

Laboratory Data.—Repeated examinations of the visual fields showed partial binasal inferior quadrantanopsia with a suggestive defect in the right temporal field (chart 1). The blindspots were enlarged, the right one more so than the left. Uncorrected visual acuity was 20/40 in the right eye and 20/200 in the left eye. Roentgenograms of the skull, sella turcica, optic foramens and chest revealed nothing abnormal. Lumbar puncture yielded clear, colorless spinal fluid under an initial pressure of 160 mm. of water. The Ayala index was 8.2. The total protein content of the spinal fluid was 52 mg. per hundred cubic centimeters. The Wassermann and Kahn reactions of the blood and of the spinal fluid were negative. Studies of the blood chemistry and of the blood cells gave normal values. The findings of gastric analysis were normal. Urinalysis revealed a 2 plus reaction for albumin and a few hyaline casts. The electroencephalographic tracings were reported to demonstrate slow abnormal waves in the right frontal area. Because of the amplitude of these

waves it was felt that they were suggestive of a deep lesion in the right frontal lobe. An encephalogram was reported to be inconclusive owing to insufficient air in the ventricular system.

Course.—On the basis of the neurologic and laboratory findings it was felt that the patient probably had a brain tumor. The diagnostic considerations favored a meningioma of the anterior fossa or a suprasellar neoplasm with parasellar extension. Operation was advised, and a transfrontal craniotomy on the right side was performed on March 27. At operation the optic nerves were observed to be thinned and tightly stretched under much enlarged, tortuous and sclerotic anterior cerebral arteries. These atherosclerotic vessels were approximately one half the size in diameter of an adult's little finger. The internal carotid arteries were likewise noted to be thickened and sclerotic. There was a prolonged postoperative convalescence owing to the development of an extradural hemorrhage and severe hypertensive crises. The patient was discharged two months after operation with

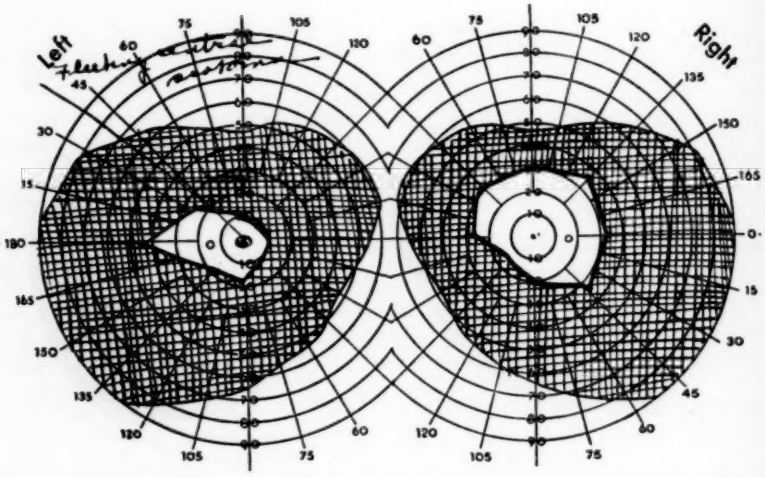

Fig. 2 (case 1).—The visual fields three months after admission, showing concentric contraction bilaterally and a fleeting central scotoma on the left.

his neurologic condition unchanged. He was last seen on Nov. 26, 1941. At this time his vision was reduced, with concentric constriction of both visual fields (chart 2). He now demonstrated deficits in recent memory and definite symptoms of personality change. Fundus examination disclosed bilateral optic nerve atrophy, more pronounced in the left eye.

The findings at operation fit in nicely with the preoperative finding relative to the visual fields, namely, a binasal field cut. Sufficient attention was not directed to this finding before operation because such a field defect could be explained only on the basis of two lesions, such as sclerosed vessels compressing the fibers of the optic nerves coming from the temporal portions of the retina. There can be no doubt that the presence of the Foster Kennedy syndrome was the most influential factor in directing the preoperative diagnosis to neoplasm.

CASE 2.—*History.*—K. K., a woman aged 49 years, was admitted to the Wills Hospital on July 16, 1940 with the complaint of impairment of vision affecting the left eye in December 1939 and the right eye more recently. The patient had been treated for arterial hypertension for the past five years. In December 1939 she suddenly experienced acute loss of vision in the left eye. This lasted one week, and gradually the vision improved. The physician who saw her at the time informed her that she had acute sinusitis and treated her for this condition. Although the vision in the eye improved, it did not return to normal. Her left eyeball seemed more prominent after this episode. Two weeks before her admission she suddenly lost the sight of her right eye. There was a gradual return of vision in this eye, but objects appeared blurred. Because of the history of sudden loss of vision and the discovery of a Foster Kennedy syndrome, the suspicion of a subfrontal neoplasm was entertained and the patient was transferred to the neurologic service at the Jefferson Hospital, on July 29.

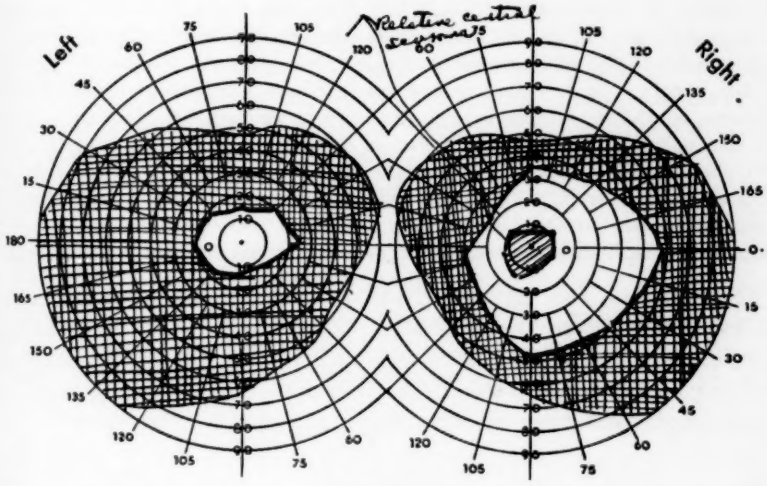

Fig. 3 (case 2).—The visual fields, showing bilateral concentric contraction, greater on the left, and a relative central scotoma on the right.

Examination.—The patient did not appear acutely ill. Physical examination revealed nothing abnormal except that her blood pressure was 200 systolic and 120 diastolic. She was alert and well oriented. There was no disturbance of olfaction. The left eyeball seemed more prominent than the right. Visual acuity was diminished markedly in the right eye and to a lesser degree in the left. The left optic disk showed primary optic nerve atrophy and the right disk some pallor, with 2 D. of papilledema. There was severe angiospasm of the retinal vessels in both eyes.

Laboratory Data.—Repeated examinations of the visual fields demonstrated severe concentric constriction of the left visual field and an early concentric constriction of the right visual field (chart 3). There was a relative central scotoma in the right visual field. The right blindspot was enlarged. Uncorrected visual acuity was 1/200 in the right eye and 20/20 in the left eye. Roentgenograms of the skull revealed nothing abnormal. Roentgenograms of the sinuses disclosed

a clouding of the frontal and maxillary sinuses. Lumbar puncture yielded clear, colorless spinal fluid under an initial pressure of 130 mm. of water. The Ayala index was 6.0. The total protein content of the spinal fluid was 39 mg. per hundred cubic centimeters. The Wassermann and Kahn reactions of the blood and of the spinal fluid were negative. The results of urinalysis and of determinations of the chemical and cellular constituents of the blood were within normal limits.

Course.—The otolaryngologist could find no evidence of active sinus disease. The significant neurologic findings consisted of the Foster Kennedy syndrome and the visual field disturbances. In view of these findings a focal lesion around the optic chiasm or in the region of the left sphenoidal ridge was suspected. This lesion was considered to be neoplasm, aneurysm or arachnoiditis. Two facts in the history were disturbing. One was the sudden loss of visual acuity on two different occasions and the other was the gradual improvement in vision after each episode. In an attempt to localize a focal lesion an encephalogram was made on August 20. The ventricles were well filled with air and were symmetric in outline; there was no displacement or any filling defect; the basilar cisterns were well visualized; the subarachnoid pathways were not well visualized. The most tenable diagnosis at this time was either chiasmal arachnoiditis or aneurysmal dilatation of sclerotic internal carotid arteries, with compression of the optic nerves. The patient was discharged unimproved on August 30. When last seen, on July 6, 1941, she revealed a recession of the papilledema in the right eye, although the disk margins were blurred. There was well marked bilateral optic nerve atrophy. Visual acuity had improved in the right eye. The concentric constrictions of the visual fields remained unchanged. The patient felt well and had no complaint.

This patient, like patient 1, had a characteristic Foster Kennedy syndrome. However, the alterations in the visual fields, in contrast to those of patient 1, were not such as to be helpful in differential diagnosis. Had not the cerebral air studies given conclusively negative results, this patient might have been subjected to an exploratory craniotomy.

COMMENT

There can be no doubt of the importance of the Foster Kennedy syndrome as a localizing lead to the presence of an expanding lesion in the anterior fossa. Many observers have confirmed the validity of the syndrome since Kennedy [2] published his paper. However, the clinician is well aware that the findings pertaining to the fundi and the visual fields must never be interpreted as isolated phenomena but in each case must be evaluated in their relationship to the other neurologic signs and symptoms. The clinician is further aware that intracranial lesions can produce bizarre combinations of objective and subjective symptoms which interfere with his preconceived ideas of diagnostic syndromes. Certainly, the value of these clinical conceptions is well borne out in the 2 cases we have described. In the first case, the dominance of the Foster Kennedy syndrome led us to a consideration of neoplasm. As later realized, the binasal field cut, the absence of olfactory dysfunction and the frontal lobe symptoms should have demanded adequate cerebral

air studies before operation. In the second case, air studies were performed because aside from the Foster Kennedy syndrome there was no evidence of an expanding intracranial lesion.

Stimulated by these experiences, we investigated the literature to determine the various reported causations of the Foster Kennedy syndrome. Kennedy [3] reported the production of his syndrome by an aneurysm of the right internal carotid artery. There was no disturbance of olfaction in his case. Cushing [4] reported the syndrome in association with a meningioma of the olfactory groove. His patient had anosmia and mental deterioration. Schmelzer [5] likewise reported the syndrome as occurring secondary to a meningioma of the olfactory groove. His patient had olfactory disturbances as well as frontal lobe symptoms. Custodis [6] reported occurrence of the syndrome secondary to a meningioma arising from the right side of the falx. Marchesani [7] listed as the possible causes of the syndrome meningiomas of the olfactory groove or of the floor of the anterior fossa, tumors and abscesses of the frontal lobe, gliomas of the intracranial portion of the optic nerves and aneurysms of the internal carotid artery. Cusick [8] reported the syndrome in association with a tumor of the cerebellum. The ventriculogram in his case demonstrated that the ocular changes were caused by the marked dilatation and forward displacement of the third ventricle. Barré and his co-writers [9] described the production of the syndrome by a craniopharyngioma with marked transfrontal extension. Schlaffer [10] has reported a case which is comparable to our first case. His patient had a Foster Kennedy syndrome with some constriction of the nasal fields of vision. A diagnosis of a neoplasm of the anterior fossa was made. At operation

3. Kennedy, F.: A Further Note on the Diagnostic Value of Retrobulbar Neuritis in Expanding Lesions of the Frontal Lobes, J. A. M. A. **67**:1361 (Nov. 4) 1916.

4. Cushing, H.: Macewen Memorial Lecture on Meningiomas Arising from the Olfactory Groove, Lancet **1**:1329, 1927.

5. Schmelzer, H.: Einseitige Stauungspapille und Störung des Geruchsinnes, Klin. Monatsbl. f. Augenh. **91**:479, 1933.

6. Custodis, E.: Meningeom der Falx und lokalisatorisch irreführendes Foster Kennedy'sches Syndrom, Klin. Monatsbl. f. Augenh. **101**:823, 1938.

7. Marchesani, O.: Symptomatologie des Nervus opticus, in Bumke, O., and Foerster, O.: Handbuch der Neurologie, Berlin, Julius Springer, 1936, vol. **4**, p. 58.

8. Cusick, P. L.: Foster Kennedy Syndrome Associated with a Tumor of the Cerebellum, Proc. Staff Meet., Mayo Clin. **13**:433, 1938.

9. Barré, J. A.; Kabaker, J., and Bruckmann: Craniopharyngiome (surtout gauche) avec énorme prolongement transfrontal (droit). Syndrome de Foster Kennedy. Troubles pyramidaux uniquement déficitaires (présentation de la pièce et de radigraphies), Rev. neurol. **69**:511, 1938.

10. Schlaffer, H.: Erwägungen über die operative Entlastung des intrakraniellen Optikusabschnittes, Med. Klin. **1**:421, 1934.

a sclerotic right internal carotid artery was discovered compressing the right optic nerve. Autopsy later revealed a marked atherosclerosis of the vessels at the base, most noticeably of the carotid arteries. The right internal carotid artery was so enlarged that it compressed the optic nerve to such a degree that the latter structure was translucent. Changes on the left side were less pronounced. Schlaffer concluded that atherosclerosis of the internal carotid arteries must be included in the differential diagnosis of the causation of the Foster Kennedy syndrome. He expressed the opinion that the presence of a nasal field defect should favor a diagnosis of arteriosclerotic disease of the carotid arteries rather than of a neoplasm. Glees [11] reported 3 cases in which he believed that the syndrome was secondary to compression of the optic nerves by arteriosclerotic vessels. He offered as an explanation of the pathogenesis of the syndrome in these cases compression of the optic nerve on one side followed by local circulatory impairment in the other optic nerve.

SUMMARY AND CONCLUSIONS

Two cases are presented in which the neuro-ophthalmologic findings conform with the syndrome described by Foster Kennedy. This syndrome has generally been considered as diagnostic of basofrontal expanding lesions. The cause of the symptom complex in both cases was non-neoplastic. The neuroretinal disturbances were a result of compression of the optic nerves by sclerotic vessels, proved in the first case and probable in the second case. The presence of a binasal field defect in association with the Foster Kennedy syndrome necessitates consideration of the diagnostic possibility of sclerotic internal carotid or anterior cerebral arteries. Some cases reported in the literature also indicate that the syndrome may be caused by an intracranial neoplasm which is not situated in the anterior fossa. In all doubtful cases of a neoplasm of the anterior fossa in which a Foster Kennedy syndrome exists, one should resort to arteriography or cerebral air studies before recommending craniotomy.

Jefferson Medical College of Philadelphia.

11. Glees, M.: Dem Foster Kennedy'schen Syndrom ähnliche Veränderungen der Sehnerven durch Arteriosklerose, Klin. Monatsbl. f. Augenh. **100**:865, 1938.

Ophthalmologic Reviews

EDITED BY DR. FRANCIS HEED ADLER

OCULOGLANDULAR TULAREMIA

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The object of the present paper is the presentation of clinical and bacteriologic data derived from 78 proved cases of oculoglandular tularemia observed in the United States and from 18 in foreign countries.

Ophthalmologists have been the first to recognize cases of tularemia in human beings in three of the nine countries in which such cases have been reported. The record is clear that D. T. Vail Sr., of the United States; Granström, of Sweden, and Pillat, of Austria, all ophthalmologists, have taken the lead in recognition of tularemia in human beings in their respective countries.

The greater vulnerability to tularemia infection of the conjunctiva in comparison with the skin is amply demonstrated by 78 ocular infections in the United States, of which only 6 were accompanied with infection of the hand although the eye and the hand in the 72 cases were subjected to the same source of infection—rabbit tissue, squirrel tissue, ground hog tissue, crushed tick or crushed fly. This greater vulnerability has given ophthalmologists an opportunity which they have grasped gloriously.

Confronted with primary ophthalmic tularemia, the ophthalmologist faces a diagnosis which is hidden in contrast to the patency of diagnosis which he encounters in the secondary ocular lesions of syphilis and of gonorrhea. Diagnosis of the latter diseases is simplified by the telltales of primary infection elsewhere in the body. As physicians, ophthalmologists take pride in their diagnoses, which demand a higher quality of alertness in the case of primary ophthalmic tularemia than in the case of the secondary ocular lesions of syphilis, of gonorrhea or of any other major infectious disease which manifests itself secondarily in the eye.

Tularemia is young, and the events of its birth, christening and adolescence have transpired within the life of the average American physician of today. For that reason I shall enumerate briefly the steps of tularemia's first recognition in eleven other countries without limiting myself to a bare recital of its strictly ophthalmologic features. These

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are only a part of the general picture of tularemia, which embraces other equally striking clinical forms.

Confusion exists over the unproved diagnoses made by Pascheff, of Bulgaria; Bayer and von Herrenschwand, in Austria; Stark, in the United States, and Aoki, Kondo and Tazawa, in Japan. Since unproved diagnoses invite lengthy but fruitless discussions, the cases reported by these authors are only enumerated and discussed briefly and are not included as proved cases of tularemia.

ANALYSIS OF SEVENTY-EIGHT AMERICAN CASES OF THE OCULOGLANDULAR FORM

Wild rabbits caused the disease in 56 cases through contact with a contaminated hand and in 2 cases by blood which spurted into the eye. Tick tissue mashed between the fingers was conveyed to the eye by the fingers in 10 cases. A fly mashed by the fingers was the cause in 1 case. Ground hog blood or bile entered the eye in 2 cases. A tree squirrel was dressed in 1 case. A dog scratch caused the disease in 1 case.

Of the patients, 61 were males and 17 females. Twenty-seven were farmers, or members of their families. There were 5 housewives, 7 students and 2 clerks, and each of the following occupations was represented by 1 patient: cook, meat cutter, sheepman, garage man, stone cutter, watchman, laborer, lumberman and motorman. The ages ranged from 2 to 72 years, with an average of 30. Five patients were under 10 years.

Conjunctivitis of animal or insect origin and unilateral enlargement of the lymph nodes which drain the infected eye constitute the dominant local picture; but this condition is accompanied by the general constitutional symptoms of fever and debility, which are a part of all forms of tularemia.

The incubation periods averaged three days, the longest being fourteen days and the shortest one day. The right eye was affected in 31 cases, the left eye in 36 cases and both eyes in 7 cases.

Unilateral enlargement of the preauricular lymph nodes occurred in 55 cases, of the submaxillary in 46 cases, of the parotid in 21 cases and of the cervical in 41 cases. Bilateral enlargement of lymph nodes occurred in 7 cases of bilateral conjunctivitis. Suppuration of some of the lymph nodes occurred in 36 cases, and absence of suppuration was reported in 20 cases. Enlargement of subtonsillar lymph nodes was reported once. Small ulcers were reported on enlarged tonsils once and on the posterior pharyngeal wall once.

Only 6 patients (7, 33, 34, 38, 46 and 64) showed coincident lesions of the eye and of the fingers which conveyed the rabbit infection to the eyes. In addition to the ulcers on the fingers, 5 of the 6 patients showed

enlargement of the axillary glands, while the sixth, patient 38, showed enlargement of epitrochlear lymph nodes.

Dacryocystitis occurred in 5 cases, in 3 of which it was purulent. One lacrimal sac required incision a year after onset. The conjunctival secretion was purulent in 5 cases. Chalazion occurred in 2 cases, chemosis in 10 cases and epiphora once (but was of long standing).

Ulcers were located on the tarsal conjunctiva in 43 cases and on the bulbar conjunctiva in 8 cases. Nodules which did not ulcerate were located on the tarsal conjunctiva in 6 cases and on the bulbar conjunctiva in 1 case.

Corneal ulcers appeared in 6 cases and in 3 left scars. One cornea was steamy. Corneal perforation, prolapse of the iris and scarring caused greatly impaired vision in case 18.

Atrophy of the optic nerve was unilateral in case 43, causing impaired vision. It was bilateral in case 46, causing complete blindness in both eyes.

Enucleation was necessary in case 54 on account of ulcer, ruptured globe and panophthalmitis.

Death occurred in 7 of 78 cases, a mortality of 9.0 per cent, in comparison with a mortality of 6.9 per cent in 15,525 cases of tularemia of all types in the United States. Death in case 63 was due to complicating bilateral pneumonia. Death in cases 9, 10 and 11 was the termination of an outbreak in a family of 4 persons who had eaten insufficiently cooked rabbit meat, patient 8 being the sole survivor.

The diagnosis was confirmed by agglutination alone in 70 of the 78 cases, by isolation of a culture from inoculated guinea pigs in 3 additional cases (1, 2 and 3), by combined guinea pig culture and agglutination in 3 additional cases and by direct culture of Bacterium tularense from the conjunctiva in the 2 remaining cases. Attempts to identify the organism from smears of the conjunctival secretion are useless. Two culture mediums are available—the coagulated hen's egg yolk of McCoy and Chapin and the blood-dextrose-cystine agar of Francis.

ANALYSIS OF EIGHTEEN FOREIGN CASES OF THE OCULOGLANDULAR FORM

Seven foreign countries have reported detailed data on 18 proved cases of the oculoglandular type of tularemia. In addition, Hüseyin (1937) furnished a composite picture of 17 cases of this type which he studied clinically and serologically in Turkey. He also gave a statistical enumeration of others, which raised the total record of cases of the oculoglandular form in Turkey to 48. Russian authors, in addition to 3 cases specifically described by Karpoff and Antonoff (1936), have mentioned "frequent cases" and "several cases" of the oculoglandular type.

In analysis of the foreign cases I shall confine myself to the data recorded for 18 cases, recorded in table 2, as follows: patients, males 10 and females 5; occupation, housewife, 4, worker 3, farmer 1, milker 1, wheel maker 1 and laboratory worker 1; cause, contact with wild hare 14 cases and a drop of culture 1; incubation period from two to twenty days with an average of seven days; eye infected, right 6 cases, left 10 and both 1; manifestations, ulcers of the conjunctiva 5 cases, an ulcerous tendency 1, nodules of the conjunctiva 6, chemosis 1, swollen lids 4, purulent conjunctivitis 1, purulent dacryocystitis 1, epiphora 1, pharyngeal angina 1 and small ulcers under the tongue 1.

The lymph nodes were enlarged as follows: preauricular 16 cases, submaxillary 13, parotid 2, axillary 2 and sternocleidomastoid 1. Suppuration of lymph nodes occurred in 6 cases but was absent in 8. The diagnosis was proved by agglutination in 12 cases, in 5 of which guinea pig inoculation with material from the eye yielded cultures of Bact. tularense. In 1 of these 5 cases, Bact. tularense was also isolated from the sternal bone marrow by guinea pig inoculation.

COMPARISON OF AMERICAN AND FOREIGN CASES

A similarity of symptoms is noted between the American and the foreign cases, but an outstanding difference is the greater virulence of the American strains, as shown by a shorter incubation period and by the presence of corneal ulcers, corneal scarring, perforation of the cornea in 1 case, impaired vision, optic nerve atrophy, blindness in 1 case, panophthalmitis requiring enucleation in 1 case and death in 7 cases. One of the deaths followed complicating bilateral pneumonia and 3 of the deaths occurred in a family outbreak caused by ingestion of insufficiently cooked rabbit meat.

The greater virulence of the American strains may be determined from table 3 by a comparison of total cases and total deaths from all forms of tularemia, which shows the American mortality to have been 6.9 per cent, while the foreign mortality was 2 deaths in 2,384 cases, or practically zero. Laboratory tests on animals of cultures received from foreign countries have all shown a much lower virulence than that of American cultures.

SUMMARY OF CASES BY COUNTRIES

United States.—The oculoglandular form of tularemia with bacteriologic confirmation was first reported by the Cincinnati ophthalmologist Derrick T. Vail Sr. (1914) assisted by Wherry and Lamb (1914 *a*). The second proved case was reported by the Cincinnati ophthalmologist Sattler (1915) and the third by the Cincinnati ophthalmologist Lamb (1917).

This array of first proved cases of human tularemia described by ophthalmologists of the University of Cincinnati College of Medicine stands as a monument to their alertness in making diagnoses clinically and bacteriologically correct of a new disease of man. How easy it would have been for them to lapse into the time-worn subservient diagnosis of "symptom syndrome of Parinaud" (1889).

In retrospect are the carefully recorded clinical observations of Ancil Martin (1925, 1926), an ophthalmologist of Phoenix, Ariz., who in 1907 described in correspondence and in medical meetings several cases observed in his practice which in the light of subsequent proved cases must be regarded as cases of oculoglandular tularemia.

Cases of the oculoglandular form multiplied in America, until Dr. Derrick T. Vail Jr. (1929) was able to collect and summarize the clinical pictures of 35. Armstrong and Kavanaugh (1932) described 5 cases encountered in their practice. Other physicians observed single cases or, rarely, 2 or 3 cases, many of which were reported in the literature. Still other physicians have not reported their cases, but since their diagnoses were proved by agglutination, they have permitted the inclusion of these cases in the present brief summary of 78 American cases, which includes those of Vail's summary. Doubtless other American cases have occurred which have not come to my attention.

Alaska.—Philip and Parker (1938) reported the isolation of Bact. tularense from rabbit ticks collected from snowshoe hares near Fairbanks, Alaska.

Japan.—Japan was the first country outside of the United States to report cases of what was proved by Francis and Moore (1926) to be tularemia. The first cases were reported by Ohara (1925 *a* and *b*, 1926 *c* and *d*) and were summarized by Francis and Moore under the convenient title "Identity of Ohara's Disease and Tularemia."

Dr. Ohara made continuous publication of his researches until by 1937 he was able to state in a personal communication to me that he had treated tularemia in 178 cases in his private hospital and that there had not been any mortality from the disease in Japan. One of these cases was of the oculoglandular type and was reported by Ohara (1930*f*) as case 14 (table 2, case 1). Ohara stated that the case had previously been reported by a physician, in November 1926 in *Grenzgebiet* (Japanese text).

Russia.—Russia in the spring of 1928 became the scene of four explosive outbreaks of tularemia in four provinces, thus being established as the third country to recognize tularemia. The source of infection in the four outbreaks was water rats, Arvicola amphibius L., which were being hunted, speared en masse and skinned for their pelts in response to a commercial demand from Europe which resulted in the collection of 4,500,000 pelts in 1927 and 1928.

TABLE 1.—*Oculoglandular Type of Tularemia: American Cases*

Case	Physician's Name and Address	Patient's: Initials, Sex and Age, Yr.	Patient's: Occupation	Source of Infection	Incubation, Days	Ocular Lesions	Enlarged Lymph Glands	Suppuration of Glands	Date of Onset	Time After Onset When Serum Agglutinated Bact. Tularense or Organism Was Isolated From Eye
1	Vail, D. T., Sr.; Wherry, W. B., and Lamb, B. H. Cincinnati	E. E. ♂ 28	Meat cutter in restaurant	Probably had dressed rabbits	.....	10 yellow deep ulcers on inflamed palpebral conjunctiva, left upper and lower lids; chemosis; purulent dacryocystitis, left eye	Left: preauricular, anterior cervical, submaxillary	No	Nov. 21, 1913	13 days, Bact. tularense isolated from eye by guinea pig inoculation
2	Sattler, R. Cincinnati	♀ 43	Farmer's wife	Had dressed a rabbit	.....	4 ulcers on conjunctiva, left upper lid, 3 on lower lid and 2 in fornix; chemosis	Left: preauricular, submaxillary, cervical	No	Oct. 1914	Bact. tularense isolated from eye by guinea pig inoculation; biopsy of nodule of conjunctiva
3	Lamb, F. W. Cincinnati	C. F. ♀	Cook	Had dressed rabbits	2	10 small deep ulcers on palpebral conjunctiva, left upper and lower lids	Left: preauricular, cervical	Yes	Nov. 12, 1916	4 days, Bact. tularense isolated from eye by guinea pig inoculation; 8 days, Bact. tularense from eye direct to culture medium
4	Martin, A. Phoenix, Ariz.	J. F. S. ♂ 33	Farmer	Had skinned jack rabbit May 14	2	Large ulcer on conjunctiva, right lower lid, and several smaller ulcers on upper lid; small abscess at inner canthus	Right: preauricular, submaxillary, anterior cervical	Yes	Nov. 16, 1925	5 days, agglutination negative; 13 days, Bact. tularense isolated from eye by guinea pig inoculation; 17 days, agglutination 640
5	Same	G. W. W. ♂ 49	Farmer	Had handled jack rabbits	.....	Ulcer on conjunctiva, right upper lid	Right: preauricular, submaxillary, anterior cervical	Yes	July 1907	18 years, agglutination 20
6	Pfunder, M. C. Miles City, Mont.	W. C. F. ♂ 63	Farmer	Removed ticks from horse with fingers April 6	2	2 small ulcers on palpebral conjunctiva, left lower lid; chemosis; steamy cornea	Left: preauricular	No	April 8, 1925	17 days, agglutination 320
7	Vail, D. T., Jr. Cincinnati	P. T. ♀ 27	Housewife	Nov. 8 dressed 2 rabbits shot by husband	2	About 10 necrotic papules and 4 ulcers on palpebral conjunctiva, both lids of right eye; also papule at limbus encroaching on right cornea; chalazion, epiphora, right eye; ulcer, left thumb; large gland in left axilla	Right: preauricular, submaxillary; left: axillary	No	Nov. 10, 1925	17 days, Bact. tularense from eye by guinea pig inoculation; 25 days, agglutination 1,280
8	Freese, H. L.; Lake, G. C., and Francis, E. Washington, D. C.	N. B. L. ♀ 6	Farmer's daughter	Had dressed and eaten wild rabbits	.....	Conjunctivitis, purulent dacryocystitis, left eye	Left: parotid, anterior cervical, submaxillary	Yes	June 29, 1925	8 days, Bact. tularense from pooled swabs of material from nose and throat by guinea pig inoculation; 36 days, agglutination 1,280
9	Same	P. J. L. ♂ 37	Farmer	Had dressed and eaten wild rabbits	.....	Bilateral conjunctivitis; swollen lids	Both sides: parotid, cervical, axillary	No	June 28, 1925	Death July 6; no autopsy

* Personal communication to the author.

vical, axillary

* Personal communication to the author.

10	Same	C. L. ♀ 7	Farmer's daughter	Had dressed and eaten wild rabbits	.....	Bilateral conjunctivitis; swollen lids	Both sides: parotid, cervical, axillary	No	June 28, 1925	Death July 6; no autopsy
11	Same	L. ♂ 2	Farmer's son	Had dressed and eaten wild rabbits	.....	Bilateral conjunctivitis; swollen lids	Both sides: parotid, cervical, axillary	No	June 28, 1925	Death July 4; no autopsy
12	Ward, W. T.* Salt Lake City, Utah	D. T. D. ♂ 60	Clerk	Shot and dressed 2 jack rabbits July 12	4	Conjunctiva, right eye, red and swollen; chemosis	Right: submaxillary, parotid	Yes	July 16, 1924	10 months, agglutination 80
13	Hubbard, E. J.* Dexter, N. M.	R. E. ♂ 19	Farmer	Killed and skinned jack rabbit June 9	3	Conjunctivitis, right eye; small ulcer, lower lid, inner canthus	Right: preauricular, submaxillary, anterior cervical, axillary	No	June 12, 1925	52 days, agglutination 640
14	Gillett, W. G. Wichita, Kan.	C. I. ♂ 15	Farmer's son	Skinned and dressed 4 rabbits Oct. 10	5	4 small ulcers on right upper lid and 3 on lower lid	Right: preauricular, submaxillary, cervical	Yes	Oct. 15, 1925	10 days, agglutination 20; 18 days, agglutination 80; 25 days, agglutination 160; 36 days, agglutination 320
15	Flick, J. B. Philadelphia	B. J. ♂ 45	Farmer	Struck in left eye with something after dressing a rabbit he had shot	1½	Conjunctivits, left eye	Left: parotid, submaxillary	Yes	Nov. 14, 1925	60 days, agglutination 160
16	Jackson, Z. W. Atlanta, Ga.	M. W. L. ♂ 18	Student	Shot and dressed a rabbit	4	Purulent conjunctivitis, left eye; ulcer on conjunctiva, left lower lid	Left: submaxillary	Yes	Jan. 2, 1926	17 days, agglutination 320
17	Pfunder, M. C.* Miles City, Mont.	M. E. ♂ 40	Rancher	Removed ticks from horse April 22 and crushed them with fingers	1	Several small ulcers on palpebral conjunctiva, right eye	Right: preauricular, cervical, submaxillary	Yes	Apr. 23, 1926	4 days, agglutination negative; 12 days, agglutination 1,280; 28 days, agglutination 1,280
18	Magath, T. B., and Yater, W. M. Rochester, Minn.	Case 3 ♂ 53	Farmer	Portion of crushed tick entered right eye	.....	Ulcer and perforation, right cornea; prolapse of iris; fusion of iris and cornea; great visual impairment	Right: preauricular, parotid, submaxillary	No	May 9, 1926	3 months, agglutination 320
19	Same	Case 2 ♂ 44	Farmer	Bitten on left cheek by a fly which he crushed, portion of which entered left eye	2-4	Conjunctivitis, left eye; small scar on cornea	Left: preauricular, parotid, submaxillary	No	June 15, 1926	50 days, agglutination 40
20	Morrison, W. R. Billings, Mont.	G.W. ♂ 38	Farmer	Handled ticks on horses	.....	Conjunctivitis, left eye; ulcer on conjunctiva, left upper lid, and on opposing bulbar conjunctiva	Left: parotid, submaxillary anterior cervical	No	June 9, 1926	4 weeks, agglutination 640
21	Same	D. W. ♂ 18	Farmer	Caught young jack rabbits	3	Conjunctivitis, left eye	Left: parotid, axillary	.....	June 1926	3d week, agglutination 80; 5th week, agglutination 1,280
22	Blakemore, W. H.* Baker, Mont.	E. B. ♂ 44	Farmer	Pulled ticks from horses	1	Conjunctivitis, left eye	Left: submaxillary, anterior cervical	Yes	June 14, 1926	19 days, agglutination 640

TABLE 1.—*Oculoglandular Type of Tularemia: American Cases—Continued*

Case	Physician's Name and Address	Patient's Initials, Sex and Age, Yr.	Occupation	Source of Infection	Incubation, Days	Ocular Lesions	Enlarged Lymph Glands	Suppuration of Glands	Date of Onset	Time After Onset When Serum Agglutinated Bact. Tularense or Organism Was Isolated From Eye
23	Carman, H. F.* Helena, Mont.	B. G. ♂ 28	.....	Questioning failed to reveal source	.....	Left eye	Preauricular	No	Nov. 1, 1926	7 days, agglutination negative; 16 days, agglutination 640
24	Clark, C. P. Indianapolis	R. H. ♂ 7	Schoolboy	None could be found	.....	Severe conjunctivitis, left eye; ulcer, left bulbar conjunctiva	Left: preauricular	.....	Dec. 1, 1926	7 days, agglutination 160
25	Junkin, H. D.* Paris, Ill.	L. S. ♂ 28	Sheep man	Tick bite of left eye	7	Severe conjunctivitis, left eye; papule, inner canthus of left eye	Left: submaxillary, buccal	Yes	May 25, 1927	Agglutination positive
26	Pfunder, M. C.* Minneapolis	J. H. B. ♂ 72	Rancher	Tick bite on abdomen; crushed a tick and fluid entered eye	2	Papule, right side of abdomen; ulcer, conjunctiva of left eye	Submaxillary	Yes	May 4, 1928	16 days, agglutination 40
27	Simpson, W. M. Dayton, Ohio	G. S. ♂ 40	Farmer	While skinning and eviscerating a ground hog, bile entered right eye from ruptured gallbladder	4	Small yellowish areas on conjunctiva of both lids, right eye	Parotid; submaxillary	Yes	May 19, 1928	8 months, agglutination 160
28	Name omitted	♂		Skinned a rabbit which he had caught April 17	3	Conjunctivitis, left eye	Left: preauricular, cervical	.....	April 20, 1928	4 days, agglutination negative; 13 days, agglutination 320
29	Blum, H. N.* New Orleans	J. deL. ♂ 42	Farmer	Skinned 2 wild rabbits	.....	Ulcers, upper and lower conjunctiva, left eye; chalazion, left upper lid	Left: preauricular, parotid	.....	June 23, 1928	Agglutination 40
30	California State Department of Health	R. M. ♂ 18	.....	Had killed and skinned rabbits and squirrels	.....	Left eye	.....	.....	June 28, 1928	21 days, agglutination 1,280
31	Pfunder, M. C.* Minneapolis	G. ♂ 36	Rancher	Pulled ticks from his body	.....	Ulcer of conjunctiva, right lower lid	Right: preauricular, submaxillary	Yes	July 1, 1928	14 days, agglutination 160
32	Marietta, S. U., Whedon, E. E.* Sheridan, Wyo.	F. G. ♂ 46	.....	Crushed ticks, which he had picked from horse, in fingers	.....	Conjunctivitis, dacryocystitis, right eye	Right: preauricular, cervical	Yes	May 20, 1928	23 days, agglutination 1,280; 50 days, agglutination 320
33	Judd, J. H. Beatrice, Neb.	T. M. ♀ 29	Farmer's wife	Skinned 5 rabbits Nov. 4	2	6 small ulcers on palpebral conjunctiva, right lower lid, and 1 on upper lid; ulcer, right index finger	Right: preauricular, anterior cervical; left: axillary	.....	Nov. 6, 1928	Agglutination positive
34	Same	F. D. ♂ 42	Garage man	While dressing rabbits Nov. 10 scratched right little finger on bone of rabbit	4	Conjunctivitis, left eye; dendritic ulcer on cornea; ulcer, right little finger	Right: axillary	.....	Nov. 14, 1928	Agglutination positive

35	Lokey, H. M.* Atlanta, Ga.	G. C. P. ♂ 37	Stone cutter	Dressed rabbits	2-3	Ulcer, left cornea; ulcers, left orbital and palpebral conjunctiva	Preauricular; submaxillary	Yes	Nov. 25, 1928	15 days, agglutination 80; Bact. tularense isolated direct from eye to culture medium
36	Name omitted	♂ 11	.....	Dressed 2 wild rabbits	4	Multiple yellow ulcers, upper right conjunctiva; chemosis	Right: preauricular, cervical	.....	Dec. 4, 1928	13 days, agglutination 320
37	Chadwick, I. B.* Coffeyville, Kan.	F. M. ♀ 27	Housewife	Dressed a rabbit June 1	3	Multiple ulcers on conjunctiva, both left lids	Left: preauricular, submaxillary, cervical	No	June 4, 1929	10 months, agglutination 320
38	Clark, W. A.* Houston, Texas	W. R. T. ♂ 27	Clerk	Dressed rabbits Jan. 12	2	Ulcer, right thumb; ulcer, left index finger; conjunctivitis, left eye, without ulcers	Both sides: epitrochlear; left: submaxillary	No	Jan. 14, 1930	18 days, agglutination 1,280
39	Hurst, V. R. Longview, Texas	P. T. ♂ 13	Schoolboy	Skinned rabbits 1 week before onset	2	Small yellow ulcers, left conjunctiva	Left: preauricular, parotid, submaxillary, cervical	Yes	Jan. 20, 1930	8 days, agglutination 10; 18 days, agglutination 5,120
40	Armstrong, R. M., and Kavanaugh, C. N. Lexington, Ky.	H. McC ♂ 14	.....	Killed a rabbit	3	Yellow nodules, palpebral conjunctiva of both lids of right eye	Preauricular; submaxillary; cervical	Yes	Aug. 1930	4 months, agglutination 1,280
41	Same	L. H. ♀ 24	.....	Dressed a rabbit Sept. 27	5	Small nodules, palpebral conjunctiva of both lids of left eye	Left: preauricular, submaxillary, cervical	Yes	Oct. 2, 1930	75 days, agglutination 320
42	Same	P. P. ♂ 26	.....	Dressed rabbits	2	3 small ulcers, lower right palpebral conjunctiva, and 1 on bulbar conjunctiva	Preauricular; submaxillary	Yes	Nov. 17, 1930	43 days, agglutination 640
43	Same	J. B. O. ♂ 38	.....	Dressed rabbits	2	Many nodules, later ulcers, on palpebral conjunctiva of both lids, right eye; optic nerve atrophy and 20/200 vision, right eye; left eye, conjunctivitis only	Preauricular; submaxillary; cervical	Yes	Nov. 23, 1930	10 days, agglutination 160; 6 weeks, agglutination 1,280
44	Same	Z. M. ♂ 40	.....	Dressed a wild rabbit	.....	Small ulcers of conjunctiva, both lids of right eye; thick membrane, palpebral and bulbar conjunctiva; chemosis	Left: preauricular, submaxillary, cervical	.....	Nov. 29, 1930	9 days, agglutination 160; death, 12th day; autopsy; pathologic report
45	Kavanaugh, C. N. Lexington, Ky.	J. I. ♂ 11	Student	Dressed rabbit caught by dog	1½	Left eye, dacryocystitis which ruptured	Left: preauricular, submaxillary, cervical	No	May 3, 1932	7 days, agglutination 160; 21 days, agglutination 640

TABLE 1.—*Oculoglandular Type of Tularemia: American Cases—Continued*

Case	Physician's Name and Address	Patient's Initials, Sex and Age, Yr.	Patient's Occupation	Source of Infection	Incubation, Days	Ocular Lesions	Enlarged Lymph Glands	Suppuration of Glands	Date of Onset	Time After Onset When Serum Agglutinated Bact. Tularense or Organism Was Isolated from Eye
46	Doyle, G. F. Winchester, Ky.	J. E. C. ♀ 61	.....	In dressing a rabbit Sept. 29, 1930 cut left index finger and before washing it rubbed both eyes	.....	Both eyes, swollen lids and mucopurulent discharge; impaired vision of both eyes, beginning Oct. 4, proceeded to complete blindness by end of eighth week, according to patient; first examination Feb. 26, 1931, showed complete atrophy both optic nerves, complete blindness and no perception of light; ulcer, left finger where cut; subcutaneous nodules, left arm and forearm; macular eruption, face and body	Both sides: axillary, preauricular, submandibular, cervical	Yes, elbow	Oct. 1, 1930	Agglutination 320
47	Huey, T. F. Anniston, Ala.	♂ 40	Farmer	Struck in left eye with piece of wood 2 days after dressing rabbit caught by dog	1	Many ulcers, on bulbar and palpebral conjunctiva, left eye; ulcer on cornea; chemosis	Preauricular; submaxillary	Yes	Nov. 23, 1930	"Agglutination positive"
48	Hodges, F. C.* Huntington, W. Va.	R. H. ♂ 12	.....	Shot and handled a sitting rabbit	.....	Right eye intensely inflamed and edematous	Parotid; submaxillary	.....	Nov. 1930	Dec. 4, agglutination 10; Dec. 8, agglutination 320
49	Theobald, G. D. Chicago	E. G. ♀ 31	Housewife	While patient was cleaning rabbit bloody water entered left eye	2	On lower left palpebral conjunctiva, 15 nodules became 15 ulcers	Left: preauricular, submaxillary, anterior cervical	.....	Nov. 16, 1930	10 days, agglutination negative; 17 days, agglutination 320; biopsy of nodule
50	Name omitted	♂ 31	.....	Shot a rabbit Nov. 22	5	Pustules and nodules of conjunctiva, both lids, right eye; dacryocystitis, right eye	Right: parotid	.....	Nov. 28, 1930	14 days, agglutination 160
51	U. S. Marine Hospital, New Orleans *	B. L. L. ♂ 52	Watchman	No rabbit contact	.....	Purulent conjunctivitis, left eye	Left: preauricular, cervical	Yes	March 2, 1931	38 days, agglutination 640
52	Blackford, S. D. University, Va.	G. C. ♀ 12	.....	Handled a living wild rabbit	2	Marked conjunctivitis, left eye	Left: parotid, anterior cervical, posterior cervical, posterior auricular	Yes	Aug. 28, 1931	3 and 6 days, agglutination negative; 14 days, agglutination 80; 19 days, agglutination 1,280; 18 months, agglutination 320
53	Campbell, E. E. Columbus, Ohio	W. J. R. ♂ 42	.....	Drop of blood entered eye while patient was dressing a rabbit	2	Lesion, lower lid of eye	Preauricular; submaxillary	Yes	Nov. 19, 1931	8 days, agglutination negative; 18 days, agglutination 160; 21 days, agglutination 1,280

54	Green, W. I.* Lawrenceville, Ill.	N. M. ♂ 23	.....	Dressed a thin rabbit killed while sitting	1	Ulcer, tarsal ligament; conjunctivitis; panophthalmitis; ruptured globe; enucleation	Preauricular; cervical	Yes	Nov. 21, 1931	2 months, agglutination 640
55	Klien-Moncreiff, B., and Rhodes, G. B. Chicago	L. C. ♂ 17	Student	Dressed rabbits in butcher shop Dec. 4	.....	Numerous nodules and 2 ulcers on palpebral conjunctiva, both left lids; 6 nodules on cornea and 3 on bulbar conjunctiva	Left: preauricular, parotid, cervical	Yes	Dec. 1931	16 days, agglutination 320; 27 days, agglutination 2,560
56	Crawford, M. Orangeburg, S. C.	J. W. ♂ 5	.....	Ate insufficiently cooked rabbit	.....	Right eye, conjunctivitis	Right: preauricular, parotid, submaxillary, cervical	Yes	Feb. 1932	3 weeks, agglutination 2,560
57	Fuller, T. E. Texarkana, Ark.	♂ 36	Laborer in sawmill	When patient crushed a dog tick between fingers, tick contents entered right eye	1	Palpebral conjunctiva of right upper lid covered with large irregular nodules, many of which bore superficial ulcers	Preauricular; parotid; anterior cervical	.....	Reported 1918	Agglutination not tested
58	Fuller *	S. R. N. ♂ 10	.....	Dressed a rabbit which his dog had caught	.....	Small ulcers on upper, lower and bulbar conjunctiva, right eye; chemosis	Right: preauricular, submaxillary	.....	April 8, 1932	1 month, agglutination 1,280
59	Hebert, L. A.* Lake Charles, La.	S. B. ♂ 52	Lumberman	Not traceable	.....	Abrasion, conjunctiva of left eye	Left: preauricular, parotid, cervical	No	Sept. 27, 1932	22 days, agglutination 320
60	Name omitted	♂ 15	Farmer	Played with small wild rabbit	.....	Yellowish papules on congested palpebral conjunctiva, both eyes	Parotid; submaxillary	No	June 4, 1933	16 days, agglutination 160
61	Hartwell, B. O.* Drexel, Mo.	W. H. W. ♀ 52	Housewife	Washed and cut up 2 rabbits	2	4 or 5 ulcers on palpebral and ocular conjunctiva, left lower lid	Left: preauricular, anterior cervical	Yes	Dec. 7, 1933	20 days, agglutination 640
62	Edmunds, M.* Petersburg, Va.	P. M. A. ♂	.....	Cleaned 2 rabbits	4-5	Several small necrotic ulcers on conjunctiva, right upper lid and 1 ulcer on bulbar conjunctiva	Right: facial, cervical	.....	Dec. 9, 1932	25 days, agglutination 40; 32 days, agglutination 320
63	Mathews, W. R. Shreveport, La.	V. M. ♂ 11	.....	Rabbit meat used for fish bait	3	Many small ulcers on conjunctiva, right lower lid; conjunctiva congested; bilateral pneumonia 11th day	Right: preauricular, parotid, submaxillary	No	June 27, 1934	8 days, agglutination negative; 20 days, agglutination 1,280; 21 days, death
64	Hensel, O., and Manheims, P. J.* New York	A. P. ♀ 32	.....	While dressing market rabbits scratched right thumb	2	Ulcer, right thumb; ulcerated papules, bulbar and palpebral conjunctiva of left eye	Right: axillary; left: preauricular, cervical	.....	Jan. 9, 1934	6 days, agglutination 4; 10 days, agglutination 80; 20 days, agglutination 5,120
65	Callaway, G. D.* Springfield, Mo.	E. B. ♂ 28	Farmer	Killed and cleaned rabbits	3	Ulcer, left cornea, with scar and 20/40 vision; superficial ulcer, upper tarsal conjunctiva	Preauricular; subtonsillar	.....	Oct. 8, 1934	16 days, agglutination 640
66	Winter, M. D.* Miles City, Mont.	R. P. ♂ 10	Student	Handled rabbits which had been cut up for dogs	.....	Ulcer on conjunctiva, left lower lid; lacrimal sac infected and incised Aug. 10, 1936	Preauricular; submaxillary	Yes	June 1935	June 8, agglutination 5,120; July 3, agglutination 2,560

TABLE 1.—*Oculoglandular Type of Tularemia: American Cases—Continued*

Case	Physician's Name and Address	Patient's Initials, Sex and Age, Yr.	Patient's Occupation	Source of Infection	Incubation, Days	Ocular Lesions	Enlarged Lymph Glands	Suppuration of Glands	Date of Onset	Time After Onset When Serum Agglutinated Bact. Tularense or Organism Was Isolated From Eye
67	Glassman, S. C.* Los Angeles	R. R. ♂ 47	Motorman	Killed and skined rabbits about Sept. 27, 1936	3	Right eye, acute conjunctivitis; yellow nodules broke down into small ulcers	Right: preauricular, submaxillary, anterior cervical	No	.....	Agglutination 1,280
68	Pfingst, A. O. Louisville, Ky.	Case 1 ♂ 22	.....	Killed and skinned rabbits	Few days	Left eye, redness and swelling, both lids; bulbar conjunctiva and cornea not involved; numerous ulcers, both lids	Left: preauricular, parotid	Yes	Aug. 1934	Agglutination negative; 10 days later, positive
69	Same	Case 2 ♂ 25	.....	Cleaned rabbits	Few days	Right eye discharged mucopus for 9 weeks; small ulcers on conjunctiva, both lids; bulbar conjunctiva and cornea not involved	Preauricular; submaxillary	Yes	Jan. 1935	Agglutination strongly positive
70	Hurst, V. R. Longview, Texas	B. M. ♂ 21	.....	Right eye injured by branch of tree Aug. 28, 1937; no mention of rabbit or other animal	.....	Large ulcer, right cornea, followed by scar in pupillary region; ulcerations, palpebral conjunctiva, right eye	Right: preauricular; submaxillary	No	Sept. 3, 1937	15 days, agglutination 640
71	Oosting, M. Galveston, Texas	F. S. ♀ 41	Housewife	Oct. 1 and 6 washed and prepared fox squirrels which husband had shot and dressed	3 or 8	Right eye, conjunctivitis, lacrimation, photophobia, swelling, mucopurulent discharge; several small ulcers on both conjunctivas	Right: preauricular, cervical, submental	.....	Oct. 9, 1937	Agglutination 320
72	Zeiter, W. J. Cleveland	♀ 53	Housewife	Cleaned market rabbit	5	Left eye, swelling, chemosis; yellow spots on conjunctiva, both lids; right hand, pustular lesions on middle finger and thumb	Preauricular; submaxillary	Yes	Dec. 21, 1937	7 days, agglutination negative; 13 days, agglutination 80; 20 days, agglutination 10,240; 34 days, agglutination 10,240; 1 yr. 8 mo., agglutination 640

73	Cramer, I. I. Cleveland	E. F. ♂ 16	Schoolboy	Hunted and dressed rabbits	2 or 6	Right lids swollen, red; palpebral conjunctiva of lower lid, 8 to 10 shallow ulcers; posterior pharyngeal wall, small shallow ulcers	Left: preauricular, anterior cervical	.....	Nov. 24, 1937	5 days, agglutination negative; 9 days, agglutination negative; 14 days, agglutination negative; 19 days agglutination 160; 21 days, agglutination 640; 24 days, agglutination 640
74	McGarvey, W. E. Jackson, Mich.	♂ 17	.....	Hunted and shot a rabbit Nov. 5, 1933	5	Redness, swelling and four grayish ulcers, upper palpebral conjunctiva of left eye; chemosis	Left: preauricular, submaxillary, cervical, axillary	Yes	Nov. 10, 1933	10 weeks, agglutination positive, 1,280
75	Goodpasture, E. W., and Dawson, J. R. Nashville, Tenn.	Z. B. ♂ 19	Farmer	Dressed wild rabbits	14	Numerous ulcers on palpebral conjunctiva, left eye, by Nov. 6	Left: preauricular, submaxillary, cervical	.....	Oct. 29, 1932	9 days, agglutination 40; 13 days, agglutination 1,280; 14 days, death, autopsy
76	Goodpasture and Dawson *	♀ 33	.....	Skinned a ground hog	.....	Purulent inflammation, conjunctiva of right eye	Right: cervical	.....	.....	6 days, agglutination negative; 11 days, agglutination 10; 11 days, death; autopsy
77	Schirmer, R., and Kimmelstiel, P.* Charlotte, N. C.	D. N. ♀ 12	.....	While patient was dressing a rabbit Oct. 30, 1940 a drop of blood entered right eye	3	Many small ulcers on conjunctiva of upper and lower lids, right eye; small superficial ulcers on markedly enlarged tonsils	Right: parotid, cervical	No	Nov. 1, 1940	14 days, agglutination 640; 64 days, agglutination 10,240; 158 days, agglutination 2,560
78	Tull, M. G.,* Ransmeier, J. C., and Ewing, C. L. Baltimore	R. S. ♂ 12	Rural inhabitant	Dog (rabbit chaser) scratched patient's face two days before onset of illness	2	Profuse purulent discharge, nasal, posnasal and from both eyes; enlarged tonsils; eyelids, both eyes, swollen and edematous; bulbar conjunctivas red and edematous; palpebral conjunctivas, numerous large and small deep ulcers; conjunctiva of right eye, granulation tissue; sight unimpaired	Both sides: preauricular, submaxillary, cervical (incised)	Yes	June 24, 1940	12 days, agglutination 640; 26 days, agglutination 163,840; 43 days, agglutination 163,840; 87 days, agglutination 10,240 (Ransmeier and Ewing p. 194)

* Personal communication to the author.

Nikanorov (1928), Suvorov, Wolferz and Voronkova (1928) and Golov and his collaborators (1928) represented the Institute of Microbiology and Epidemiology for the Southeast of Russia, located at Saratov. They reported 150 cases in the province of Astrakhan, on the Volga; 100 cases in the province of Uralsk, on the banks of the Ural, and 800 cases in the province of Ryazan, on the bank of the Oka, which is a tributary of the Volga. There were no deaths.

Sarchi (1929, 1930), with headquarters in the Division of Epidemiology, Sanitary-Bacteriologic Institute of Sverdlovsk, reported 76 cases of tularemia in the village of Muji, which is on the river Ob 180 kilometers south of Obdorsk, which is located in Siberia at the intersection of the Arctic Circle and the Ob.

Sarchi (1930) stated that the oculoglandular type was particularly frequent.

Golov, Kniazevsky, Berdnikov and Tiflov (1928) reported 2 cases of the oculoglandular type.

Berezin (1934) stated that there were several cases of ocular infection among workers canning rabbit meat and that 1 patient, aged 24, working in the canning factory at Kurgan, came to the surgical clinic March 22, 1932 with mild ocular symptoms.

Karpoff and Antonoff (1936) reported 43 cases of tularemia observed in 1935 in a water-borne epidemic in Siberia, of which 3 were of the oculoglandular type (table 2, cases 15, 16 and 17). The source of infection was the drinking of water from a stream in which Bact. tularense was demonstrated. Presumably the water became infected by water rats and mice, although none of these animals were seen in the water at the time of the investigation.

Norway.—Thjøtta (1930, 1931) was the first to recognize tularemia in Norway. His first patient (Dr. B. H.) shot and dressed a wild hare on a hunting trip Sept. 3, 1929, became ill September 6 and had typical ulceroglandular tularemia, which Thjøtta proved serologically by the agglutination of Bact. tularense in December 1929, the reaction being positive at a dilution of 1:1,280. During 1930 Thjøtta diagnosed 50 cases of tularemia in Norway.

Bryn (1930), of Trondhjem, reported the first known case of the oculoglandular type of tularemia noted in the early active stage in Scandinavia or other parts of Europe (table 2, case 2).

Canada.—McNabb (1930) reported the first proved case of tularemia in Canada in a miner living near Timmons, Ontario. Parker, Hearle and Bruce (1931) first proved the infection in Canadian fauna by isolation of the organism from a sick snowshoe hare found in British Columbia and from the rabbit ticks which infested the hare.

Sweden.—Granström (1931, 1932), an ophthalmologist of Stockholm, was the first to recognize tularemia in Sweden in a case of the

oculoglandular form and in 2 associated cases of the ulceroglandular form. The patient cut up a rabbit Feb. 13, 1931, became ill February 17 and was admitted to the ophthalmic clinic March 11 (table 2, case 3). The patient's wife and the market man who skinned the rabbit acquired typical ulceroglandular tularemia.

Olin (1938*a*) mentioned statistically an additional case of the oculoglandular type. He placed the number of known cases of tularemia in Sweden at 200, without a death.

Olin (1938*b*) furnished the first direct cultural proof of tularemia in naturally infected lemmings, which were dying in 1938 in an epidemic at Arjeplog, Sweden, a few miles south of the Arctic Circle; the lemming had been strongly suspected by Thjøtta as a source of human tularemia in Norway.

Austria.—Pillat and David (1936, 1937) reported the first proved case of tularemia in Central Europe; it was of the oculoglandular type.

W. A., aged 24, a milker in a dairy in Lower Austria, had conjunctivitis of the left eye Sept. 4, 1935 and entered the ophthalmic clinic of Vienna September 11 (table 2, case 4). He had dressed a wild hare caught with the hands 30 kilometers from Vienna, near the Czechoslovakian border at Fuchsenbigl, in the district known as Marchfeld. Bact. tularense was isolated from the conjunctival material by guinea pig inoculation on the seventeenth day of illness, and the serum agglutinated Bact. tularense in a dilution of 1:400 on the forty-sixth day.

Hamburger (1937) reported 3 proved cases of oculoglandular tularemia observed in the ophthalmic clinic of Vienna, with the technical assistance of David. Two patients had dressed wild hares in the northeastern section of Lower Austria, at Drösing and Reinthal, and the third had eaten rabbit in Vienna (table 2, cases 5, 6 and 7).

Emphasis should be placed on the leadership of the ophthalmologists of Vienna Pillat and Hamburger for recognition of the oculoglandular type of tularemia in Austria in advance of 70 cases of the commoner, ulceroglandular type reported during the following year by physicians of northeast Lower Austria and traced to wild hares. That the nature of the epidemic in all its ramifications could be grasped so rapidly and so correctly is to the credit of the thorough bacteriologic and serologic work done by Professor David.

Arzt (1938) reported a proved case of the oculoglandular type in a patient from Dürnkrut, on the March River in Lower Austria, who came to the dermatologic clinic on Feb. 2, 1937 (table 2, case 8). The agglutination test in this case, done by David, gave a positive result at a dilution of 1:1,280. Arzt observed a total of 15 cases of tularemia in the 1936-1937 season, only 1 of which was of the oculoglandular type.

TABLE 2.—*Oculoglandular Type of Tularemia: Foreign Cases*

Case	Physician's Name and Address	Patient's Initials, Sex and Age, Yr.	Patient's Occupation	Source of Infection	Incubation, Days	Ocular Lesions	Enlarged Lymph Glands	Suppuration of Glands	Date of Onset	Time After Onset When Serum Agglutinated Bact. Tularense or When Organism Was Isolated from Eye
1	Ohara, H. Fukushima, Japan	(Case 14) ♂ 19	Farmer	Dressed a rabbit found dead	10	Left eye, conjunctivitis, ulcer on lower palpebral conjunctiva near edge of lid	Left: submaxillary; preauricular	Yes	Oct. 1926	.....
2	Bryn, A. Trondhjem Norway	♂ 45	.....	Dressed a rabbit which he shot Feb. 16, 1930	8	Right eye, conjunctivitis; shallow ulcers, lower lid	Right: preauricular, submaxillary	No	Feb. 24, 1930	10 days, agglutination negative; 21 days, agglutination 160
3	Granström, K. O. Stockholm, Sweden	K. P. ♂ 45	.....	Cut up a rabbit bought in the market	4	Small ulcer on palpebral conjunctiva, left lower lid; small nodules on conjunctiva of both lids	Left: preauricular	.....	Feb. 17, 1931	Agglutination 640
4	Pillat, A., and David, H. Vienna, Austria	W. A. ♂ 24	Milker in a dairy	Dressed a wild hare caught 30 kilometers from Vienna near the Czechoslovakian border at Fuchsenbigl, Austria	3½	Yellowish gray nodules on palpebral and ocular conjunctiva, left eye	Left: preauricular; superficial glands of entire body	No	Sept. 4, 1935	17 days, Bact. tularense from eye by guinea pig inoculation; 46 days, agglutination 400
5	Hamburger, F. A. Vienna, Austria	W. U. (case 1) ♀ 28	Housewife	Oct. 22, 1936 cooked a rabbit which her husband had found in a field in Drösing, Austria	2	2 pea-sized ulcers on upper and 2 on lower lid, right eye	Right: preauricular, submaxillary	No	Oct. 22, 1936	12 days, Bact. tularense from eye by guinea pig inoculation; 18 days, agglutination 160; 29 days, agglutination 320; 53 days, agglutination 1,280; 70 days, agglutination 640
6	Same	T. K. (case 2) ♀ 37	Housewife	Oct. 21, 1936 dressed a rabbit which her sons had found dying in the woods in Reinthal, Austria	6	Several small ulcers with ragged edges, left upper lid; bulbar chemosis; inflamed papillary hypertrophy of conjunctiva of both lids	Left: preauricular, submaxillary	No	Oct. 27, 1936	18 days, Bact. tularense from eye and from marrow of sternum by guinea pig inoculation; 18 days, agglutination 160; 24 days, agglutination 640; 31 days, agglutination 1,280; 54 days, agglutination 1,280
7	Same	K. H. (case 3) ♂ 13	.....	Ate roast rabbit Dec. 25, 1936 in Vienna	16	Jan. 10 patient noticed reddening and swelling of right eyelid; conjunctiva studded with small yellowish gray nodules which did not ulcerate	Right: preauricular, submaxillary, sternocleidomastoid	No	Jan. 10, 1937	32 days, Bact. tularense from eye by guinea pig inoculation; 32 days, agglutination 160
8	Arzt, L. Austria	S. M. ♀ 56	.....	Dressed a hare Dec. 11, 1936 at Dürnkrut, Austria	7	Right eye, purulent conjunctivitis; palpebral conjunctiva studded with multiple follicular swellings	Right: preauricular, submaxillary	Yes	Dec. 18, 1936	60 days, agglutination 1,280

9	Netoušek, M., and Kollár, J. K. Bratislava, Czechoslovakia	S. D. ♂ 35	Wheel maker	Skinned and ate rabbit found dead	3	Lesions on lids, left eye	Left: pre-auricular, submaxillary, axillary	Yes	Feb. 5	20 days, agglutination 1,280
10	Same	J. S. ♀ 25	House-wife	Prepared for eating rabbit found dead	7	Lids of left eye swollen	Left: pre-auricular	Yes	Jan. 1937	25 days, agglutination 1,280
11	Same	P. Z. ♂ 48	Worker	Skinned rabbit found dead; wife and 2 children also sickened	7	Lids of left eye swollen	Left: sub-maxillary, axillary	No	.....	Agglutination 2,560
12	Same	D. S. M. ♂ 20	Worker	Skinned a rabbit	20	Lids of left eye swollen	Left: pre-auricular, submaxillary	No	.....	Agglutination 1,280
13	Same	A. P. ♀ 26	House-wife	Ate a rabbit	3	Phlyctenular conjunctivitis	Left: pre-auricular, submaxillary	Yes	Dec. 16, 1936	.....
14	Same	S. K. ♂ 50	Worker	Caught a rabbit and skinned it	.....	Right eye swollen	Right: pre-auricular, submaxillary	No	Dec. 15, 1936	Agglutination 1,280
15	Karpoff, S. P., and Antonoff, N. I. Tomsk, Russia	(Case 1)	.....	.....	.....	Right eye, photophobia, epiphora, redness of conjunctiva; yellowish grains, lower lid	Preauricular	.....	1935	.....
16	Same	(Case 2)	.....	.....	.....	Left eye, same symptoms as in case 16; pharyngeal angina	Left: pre-auricular; parotid region	.....	1935	.....
17	Same	(Case 3)	.....	.....	.....	Left eye, conjunctivitis; small ulcers under tongue	Left: pre-auricular, submaxillary	.....	1935	.....
	Hüseyin, K. Constantinople, Turkey	(17 cases)	.....	Undetermined	.....	Composite picture: monocular intense conjunctivitis; edematous eyelids; millet seed follicular conjunctivitis; yellow oval ulcers; purulent dacryocystitis once	Preauricular; submaxillary; anterior cervical	Yes	1936	.....
18	Kamil, S., and Bilal, S. Constantinople, Turkey	S. B ♂	Laboratory worker; veterinarian	A drop of culture splashed into left eye	2	Left eye, watering and conjunctivitis with tendency to formation of ulcers	Parotid; submaxillary	Yes	March 1937	30 days, agglutination 8,000; Bact. tularense isolated from eye

Czechoslovakia.—Tularemia was first recognized in Czechoslovakia during the hunting season from November 1936 to January 1937, when an outbreak of human tularemia was reported along the Austrian-Czechoslovakian border in the provinces of Lower Austria, in Austria, and in the provinces of Moravia and Slovakia, in Czechoslovakia. The Morava River in its upper part separates Moravia from Slovakia and in its lower part separates Slovakia from Lower Austria, but under the German name of March River, before emptying into the Danube.

Tománek (1937) reported that an epizootic in hares started in Czechoslovakia in October 1936 and that an epidemic of tularemia in human beings began about the end of December 1936.

Drbohlav (1937) reported 416 cases for Czechoslovakia as follows: Moravia 290 cases, Slovakia 119 cases and Bohemia 7 cases.

Netoušek and Kollár (1937) observed 13 cases of tularemia in a clinic in Slovakia, 7 of which were of the oculoglandular type. All the patients had passed through the febrile period before admission to the clinic.[1]

Turkey.—Turkish Thrace, in Europe, was the scene of an epidemic of 150 cases of tularemia from June to September 1936. The epidemic was recognized by the military physicians Bican, Titiz and Kurtaran, of the military garrison at Lüleburgaz, in Thrace, and affected 133 soldiers of the garrison and 17 civilians living near Lüleburgaz.

Hüseyin (1937) made bacteriologic investigations in 1936 on patients of the Lüleburgaz epidemic; he was the first to furnish proof of tularemia in Turkey. He obtained definite agglutination of Bact. tularense in 13 of the cases and isolated by mouse inoculation from a Thracian patient a culture which he designated the Gülhane strain after the Gülhane hospital, in Constantinople, where he worked. He studied clinically and serologically 75 of the Lüleburgaz patients, of whom 17 had the oculoglandular type. Of the first 4 patients studied, 1 had severe conjunctivitis and suppuration of the regional lymph nodes, while the other 3 showed only swelling and suppuration of the submaxillary lymph nodes and of the lymph nodes of the neck. The symptoms began with intense inflammation and swelling of the eyes and scanty discharge. After the edema disappeared, on about the tenth day, the conjunctiva presented millet seed follicles, which were followed by yellow oval ulcers in a few cases. Simultaneous infection of the two eyes was not observed, nor were there severe complications in the eyes. There was always swelling of the regional lymph nodes—preauricular, submaxillary or anterior cervical. Purulent dacryocystitis developed

1. Dr. Vladimír Palic, attaché of the Czechoslovakian legation in Washington, D. C., translated the data on the cases of the oculoglandular form (table 2, cases 9, 10, 11, 12, 13 and 14).

TABLE 3.—*World Distribution of All Forms of Tularemia*

Date of First Proof of Tularemia	Total Cases to 1941	Total Deaths to 1940	Authors Who First Proved Tularemia in Various Countries	Oculoglandular Form of Tularemia; First Reported and Proved Cases
United States 1911	15,470	967	McCoy (1911) McCoy and Chapin (1912 *a* and *b*)	1 by Vail (1914) and Wherry and Lamb (1914 *a*) 1 by Sattler (1915) 1 by Lamb (1917) 78 subsequent cases in table 1
Japan 1925	178	0	Ohara (1925 *a* and *b*; 1926 *c* and *d*) Francis and Moore (1926)	1 by Ohara (1930 *f*)
Russia 1928	1,169	0	Nikanorov (1928) Wolferz (1928) Suvorov and associates (1928) Golov and associates (1928) Sarchi (1929, 1930)	2 by Golov and associates (1928) "Frequent cases" by Sarchi (1930) "Several cases" by Berezin (1934) 3 by Karpoff and Antonoff (1936)
Norway 1929	50	0	Thjøtta (1930, 1931)	1 by Bryn (1930)
Canada 1930	21	0	McNabb (1930) Parker and associates (1931)	
Sweden 1931	200	0	Granström (1931)	1 by Granström (1931) 1 by Olin (1938 *a*)
Austria 1935	200	1	Pillat and David (1936) David (1937)	1 by Pillat and David (1936, 1937) 3 by Hamburger (1937) 1 by Arzt (1938)
Czechoslovakia 1936	416	0	Drbohlav (1937) Tománek (1937)	6 by Netoušek and Kollár (1937)
Turkey 1936	150	1	Hüseyin (1937) Arar (1937) Gotschlich and Berkin (1938) Kamil and Bilal (1938)	48 by Hüseyin (1937), Arar (1937), Gotschlich and Berkin (1938) 1 by Kamil and Bilal (1938)
Italy 1931	1 hare	.....	Bardelli and Ravaglia (1931)	
Alaska 1937	rabbit ticks	.....	Philip and Parker (1938)	
Germany 1939	1 hare	.....	David and Schiessler (1939)	
Questionable Diagnoses in Cases in Which a Diagnosis of Tularemia Was Not Recognized, Reported, Proved by Culture or Confirmed by Agglutination				
Bulgaria	4	0	Pascheff (1915 to 1926)	4 of oculoglandular type of Pascheff's disease
Austria	2	0	Bayer and von Herrenschwand (1919) von Herrenschwand (1935)	2 of oculoglandular type of pseudotuberculosis rodentium
United States	4	0	Stark (1924)	4 of oculoglandular type of Pascheff's disease
Japan	9	0	Aoki, Kondo and Tawaza (1925), (1928); cases ascribed to "filterable virus"	

in 1 case. There were no deaths from any type of the disease. Not a single case could be traced to contact with wild hares.

Arar (1937) and Gotschlich and Berkin (1938) in a summary of the 150 cases classified the condition in 48 as oculoglandular, in 88 as glandular, in 14 as ulceroglandular and in none as of the typhoid type. They stated that there was one death during the entire epidemic, but details concerning it were not given. They stated that among the

soldiers of Lüleburgaz it was not possible to secure any history of contact with rabbits, hares or other known animal vectors of tularemia.

Kamil and Bilal (1938) reported on a patient with laboratory infection of the oculoglandular type in the person of Bilal (table 2, case 18). Seven months after he started his laboratory studies, a drop of culture splashed into Bilal's left eye. After an incubation of forty-eight hours there were fever and watering of the eye followed by conjunctivitis which had an ulcerous tendency. The parotid and the submaxillary lymph nodes became tender and swollen and suppurated. The blood serum agglutinated Bact. tularense April 23, 1937 in a dilution of 1:8,000. A culture of Bact. tularense was isolated from his eye by Kamil.

The source of the 1936 epidemic and the mode of transfer to human beings were not satisfactorily proved, although two strains of Bact. tularense were isolated in 1937 from the water of the brook Kaynarea, which flows past Lüleburgaz and several other tularemia-infected localities, a fact which raised the question of drinking water as a source of the infection. One of these strains was isolated by Öz and the other by Hüseyin (Öz, 1938; Gotschlich and Berkin 1938, supplement).

Italy.—Bardelli and Ravaglia (1931) reported the isolation of Bact. tularense from the bone marrow of a decomposed hare found dead during an epidemic in a hunting reserve located in the province of Rovigo. The culture which they sent to me was Bact. tularense but of low virulence.

Central Germany.—Henninger (1937) at the seventeenth session of the *Deutschen Vereinigung für Mikrobiologie* Sept. 20 to 22, 1937, in Berlin, presented a seven year chronologic summary of watchful observations and investigations of man and rodents in Germany to detect the first appearance of tularemia, but proof had not been obtained.

In 1939, however, the rodent reservoir of infection in hares was positively established by David and Schiessler (1939), of Vienna. They were the first to furnish direct proof of tularemia in Germany, by their isolation of Bact. tularense from a wild hare trapped in a game preserve at Nuremberg, Bavaria. There have not been subsequent reports of tularemia in Central Germany.

PASCHEFF'S DISEASE

Dr. C. Pascheff (1915 to 1926), of Sofia, Bulgaria, observed 3 cases in 1915 and 1 in 1916 of a disease of the conjunctiva which he claimed was new and which he called "conjunctivitis necroticans infectiosa" (table 4, cases 1, 2, 3 and 4). His preliminary report described the onset with chills, headache and fever and localization in the conjunctiva of one eye. The lids were swollen. Numerous white

TABLE 4.—*Pascheff's Disease and Pseudotuberculosis Rodentium*

Case	Physician's Name and Address	Patient's Initials, Sex and Age, Yr.	Occupation	Source of Infection	Incubation, Days	Ocular Lesions	Enlarged Lymph Glands	Suppuration of Glands	Date of Onset	Time After Onset When Serum Agglutinated Bact. Tularense or When Organism Was Isloated from Eye
1	Pascheff, C. Sofia, Bulgaria	D. P. B. (case 1) ♂ 30	.....	Patient mentioned cats	..	Right eye, conjunctivitis; lids swollen; several small ulcers of conjunctiva	Right: preauricular, submaxillary	Yes	Dec. 14, 1914	
2	Same	Mme. C. (case 2) ♀ 40	.....	.....	..	Left eye, conjunctivitis; lids swollen; white spots on conjunctiva	Left: preauricular, submaxillary	Yes	Dec. 18, 1914	
3	Same	P. T. (case 3) ♂ 45	Professor	Had worked with wood in cellar	..	Left eye, conjunctivitis; white spots on conjunctiva, some of which ulcerated	Left: preauricular, submaxillary	Yes	Aug. 9, 1915	
4	Same	K. (case 4) ♂ 32	.....	.....	..	Left eye, lids swollen; on conjunctiva small white superflical spots which ulcerated	Left: preauricular, submaxillary, parotid	No	Aug. 1916	
5	Bayer, G., and von Herrenschwand, F. Innsbruck, Austria	A. F. (case 1) ♂ 21	Soldier	Occupied a cave on Italian front several days and nights; in cave were many rats, mice and dormice	..	Dec. 2, left eye, grayish white nodules with crater-like surfaces at fornix and on tarsal conjunctiva; ulcers on conjunctiva of upper lid, grayish white	Left: preauricular, submaxillary, parotid	Yes	Nov. 25, 1917	
6	Same	G. B. (case 2) ♂	Physician; co-author	Accidental laboratory infection caused by strain isolated in case 1; material from infected guinea pig squirted into right eye from defective syringe Feb. 27, 1918	4	Right eye, conjunctivitis; swollen eyelids; yellow nodules on conjunctiva, lower lid of right eye	Right: preauricular	No	March 3, 1918	16 years after onset, agglutination 160, according to Henninger (1937)

spots were scattered over the red conjunctiva throughout. They were round or elongated and had irregular edges, and some ulcerated. The white spots disappeared in two to three weeks, and the ulcers healed. Lymph nodes on the side of the infected eye—preauricular, submaxillary and parotid—became swollen and suppurated and healed in two to three months. There were no corneal complications. Guinea pigs inoculated subcutaneously with spots excised from the conjunctiva died in seven to eight days and at autopsy showed white spots on the liver and, especially, on the spleen. They also showed glandular swelling. Sometimes there was extensive necrosis or infarcts of the liver. The white points in the spleens and lymph nodes were necrotic foci histologically. "Micrococcobacillus polymorphus necroticans," according to Pascheff, was the cause of the disease.

My suggestion to Professor Pascheff in 1926 was that cultures of material from his patients and guinea pigs and tests for agglutination of Bact. tularense by serum from his patients would definitely settle the question of the relation, if any, of the disease to tularemia and that clinical and pathologic comparisons would never settle it. As yet I have never seen any reports of tests for the agglutination of Bact. tularense by serums of patients suffering from Pascheff's disease, nor have I seen reports of cases of this disease other than Pascheff's cases of 1915 and 1916 and the 4 cases reported by Stark (1924).

Stark (1924), under a diagnosis of Pascheff's disease, reported 4 cases from El Paso, Texas, which he had observed within the preceding seven years. All the patients lived in rural areas, but a history of animal infection through rabbits or squirrels was not obtained, nor were agglutination tests for Bact. tularense made. The patients showed ulcers on the tarsal conjunctiva and enlarged glands in the preauricular, parotid and submaxillary regions.

DISEASE DUE TO A FILTRABLE VIRUS

Aoki, Kondo and Tawaza (1925, 1928), of Japan, observed 9 cases in human beings of a disease of hares which they ascribed to a filtrable virus. They conducted extensive bacteriologic investigations on human beings, rabbits, guinea pigs, mice and white rats. They were never able to stain or cultivate the virus, which they grouped with the filtrable viruses. Their final statement was that the virus was similar to the filtrable virus of encephalitis lethargica.

PSEUDOTUBERCULOSIS RODENTIUM

Bayer and von Herrenschwand (1919) reported "concerning the inflammation of the conjunctiva (Parinaud's conjunctivitis) called forth by bacteria belonging to the group of the Bacillus pseudotuberculosis

rodentium." Their report, covering thirty-two pages, is based on the following 2 cases (table 4, cases 5 and 6):

CASE 1.—A. F., a soldier aged 21, entered the ophthalmic clinic of Bayer and von Herrenschwand in Innsbruck, Austria, Dec. 1, 1917. The illness had appeared Nov. 25, 1917 after the patient spent several days and nights on the Italian front in a cave located in the province of South Tyrol, Austria. The cave was densely populated with rats, mice and dormice. The left eye showed grayish white nodules with crater-like surfaces located at the fornix and on the tarsal conjunctiva. The preauricular, submaxillary and parotid lymph nodes on the left side were swollen and later suppurated. The right eye remained well.

CASE 2.—Prof. G. Bayer (one of the authors) became ill March 3, 1918, four days after accidental inoculation of his right eye with material from a guinea pig ill with the virus from patient 1. The inoculum had squirted into his eye from a defective syringe February 27. His right eye showed swollen lids, conjunctivitis and yellow nodules on the conjunctiva of the lower lid. The right preauricular lymph node enlarged but did not suppurate.

The authors investigated these cases in great detail along clinical, pathologic and bacteriologic lines but left the question of the definite inciting agent in a confused state, nullifying a specific etiologic diagnosis.

They reported the isolation in pure culture of a *Varietät* of B. pseudotuberculosis rodentium as the causative organism in their 2 cases. This is the nearest commitment they make to a specific causative organism. Without naming their organism they classified it as a member of what they called the B. pseudotuberculosis rodentium group and further defined that group as comprising Bacillus pestis, Bacterium septicaemia hemorrhagica and B. pseudotuberculosis rodentium. They preferred to follow Parinaud (1889 *a* and *b*) and Pfeiffer (1889) and to accept group diagnosis in preference to specific causative micro-organisms. They preferred the dawn to the maturity of bacteriology.

They quoted freely from reports of the fundamental discovery of Bact. tularense by McCoy and Chapin (1912 *a* and *b*), of its growth on coagulated egg yolk and of its confirmation by Vail (1914), Sattler (1915), Lamb (1917) and Wherry (1914). But they followed their quotations from these investigators by slighting references to "the superfluous setting up of new diseases" and to "micro-organisms thought to be their causative agent." They claimed to have demonstrated that Vail, Sattler and Lamb were dealing with *Varietäten* of B. pseudotuberculosis rodentium. Nowhere in their thirty-two pages did they designate their organism as Bact. tularense, although they used coagulated egg yolk culture medium.

Von Herrenschwand (1935) made a second report on the 2 cases under the title "Parinaudsche Conjunctivitis—Tularaemia oculoglandularis." In this report, covering forty-four pages and made sixteen years after the first, he clung to the original group diagnosis of the causative micro-organism. A third case was described for the

first time, that of von Herrenschwand himself, who contracted a laboratory infection in 1918 while working with material from his two patients. His illness was characterized by a shallow aphthous ulcer on the lower lip, swelling of the regional lymph glands, fever, diarrhea and weakness, and it lasted fourteen days although the onset was completely unnoticed.

A serologic diagnosis by means of the agglutination test was reported in the cases of Bayer and von Herrenschwand by Henninger (1937), who obtained agglutination of Bact. tularense by serum collected in 1932-1933. The serums agglutinated the organism in a dilution of 1:80 and 1:160, respectively, sixteen years after the onset of the infection. Commenting on Henninger's finding, von Herrenschwand reported, "And so, our pseudotuberculosis strain is unmasked as Bact. tularense."

Von Herrenschwand's ready conversion to the belief that Bact. tularense instead of B. pseudotuberculosis rodentium was the causative organism in these particular cases on the basis of the serologic agglutination tests made by Henninger calls attention to the inconsistency that his now called "Bact. tularense strain" grew on ordinary culture medium—which Bact. tularense does not do. For this anomaly he offered the convenient explanation that between B. pseudotuberculosis rodentium and Bact. tularense there stand intermediate connecting strains of Bact. tularense which occasionally grow on ordinary culture medium. Nobody who has worked with Bact. tularense would agree with that view. Befuddlement of mind in distinguishing between B. pseudotuberculosis rodentium and Bact. tularense has not come to my attention in any other publication. I can see no reason for clothing bungling bacteriology with respectability. Professors who are at home at the bedside may easily become lost in the field of refined bacteriology.

Von Herrenschwand, clinging to clinical pictures, proposed the adoption of double names joined by hyphens, thus: "Parinaudsche conjunctivitis-tularaemia oculoglandularis" or "tularaemia oculoglandularis-Parinaudsche conjunctivitis." He proposed this hyphenization and subjoining of names for the sake of honor to Parinaud. But words without works are empty honor.

One can best honor the name of Parinaud in helping, by scientific research, to solve the problem of etiology which confronted him in 1889. When by research one cleaves the inclusive clinical picture of Parinaud's conjunctivitis into different bacteriologic entities, then one really honors the name of Parinaud, and McCoy and Chapin did exactly that by their discovery of Bact. tularense in 1912. More effort in the field of etiology should reduce the number of nebulous diagnoses of Parinaud's conjunctivitis to the vanishing point, and then honor of the name of Parinaud will be complete without hyphenization.

In this connection allow me to quote the particularly sane words of Pillat, from Pillat and David (1937): "We are not justified in longer retaining the name of a disease which, so to speak, dated back to a prebacteriologic era, since now modern methods enable us to use an etiologic designation."

Von Herrenschwand slightingly referred to McCoy's discovery of tularemia as a "rediscovery" and insisted that priority and first description must emphasize Parinaud. This view simply reiterates von Herrenschwand's contention of the superiority of clinical picture over bacteriologic differentiation.

Von Herrenschwand stated that "tularemia in America sailed under false colors up to the discovery of the agglutination test in 1919." Regarding this statement I refer him to the article by McCoy and Chapin (1912 *a*) in which the announcement of the discovery of Bact. tularense and of its agglutination by the serums of 2 patients with tularemia contracted in the laboratory were coincident. That publication contains a table showing that 11 human serums were tested for agglutination of the newly discovered Bact. tularense. Nine of these serums served for negative controls and failed to agglutinate the organism, but 2, collected from Chapin (C. C.) and his laboratory assistant (E. T.), did agglutinate it, one in a dilution of 1:1,250 and the other in a dilution of 1:1,000, thus giving serologic proof of the first 2 cases of laboratory infection with Bact. tularense seven years before the date (1919) claimed by von Herrenschwand. The official records show that ninety-four days after beginning work in the San Francisco plague laboratory with animals infected with tularemia Dr. Chapin was granted twenty-eight days' leave of absence, beginning March 1, 1911, on account of sickness. The illness was accompanied by fever and was unaccompanied by glandular enlargement or other lesions and incapacitated Dr. Chapin for all duty for twenty-eight days. Shortly after returning to duty Dr. Chapin discovered the positive response to the agglutination test by his own serum and by that of his assistant.

This was the initial discovery and application of the agglutination test for the diagnosis of tularemia in man.

PARINAUD'S CONJUNCTIVITIS

Bayer and von Herrenschwand (1919) mentioned Parinaud and Parinaud's conjunctivitis fifty-two times. Von Herrenschwand (1935) made the same mention forty-six times. Much retrospect reasoning was employed in an effort to show that the disease in Parinaud's cases was due to B. pseudotuberculosis rodentium, all of which is bookish conjecture.

Parinaud (1889 *a*) at the Feb. 5, 1889 meeting of the Ophthalmological Society of Paris made his first brief report, which was amplified and published the same year. He stated that within a period of four years he had observed 3 cases of granular conjunctivitis which he thought to be of animal origin. One patient was a butcher, and the other 2 were women. The disease was monocular, did not involve the cornea, caused swelling and suppuration of the lymph nodes of the corresponding parotid region, was accompanied by fever and healed spontaneously after three to five months.

Parinaud's report stimulated similar reports of Parinaud's conjunctivitis by physicians of France and other countries, who named any animals with which the patient had had contact. The animals included cattle, hogs, horses, sheep, cats, dogs, rats and birds, all of which are known to be either nonsusceptible to tularemia or only slightly susceptible. In all the years there has not been a report of human or rodent tularemia in France, the land of Parinaud.

Parinaud's conjunctivitis is a frequent diagnosis in the United States, but in the negative sense, signifying absence of knowledge of the exciting cause. In 1928 I began testing serums collected from patients whose condition was diagnosed Parinaud's conjunctivitis at the Manhattan Eye, Ear, and Throat Hospital, New York, but all of them have failed to agglutinate Bact. tularense. New York city increased in population from 6,500,000 in 1928 to 7,500,000 in 1939. During that period 46 proved cases of tularemia were reported in the city, all of which were of the ulceroglandular type, although 1 was of both the ulceroglandular and the oculoglandular form (table 1, case 64). All the patients had skinned, dressed or otherwise prepared wild rabbits shipped to the municipal market of that city from states west or southwest of the state of New York.

Physicians of New York city were made tularemia conscious with the city's first report of tularemia in 1928 and have been kept tularemia conscious for thirteen years by repeated reports of the disease in medical journals. While they have reported only 1 case of oculoglandular tularemia in New York city during that time, the clinical diagnosis of Parinaud's conjunctivitis has continued to be made there in its usual normal frequency.

Dr. A. A. Eggston, pathologist to the Manhattan Eye, Ear, and Throat Hospital, recently informed me that he does not recall having noted a case of oculoglandular tularemia in his twenty-two years of service in that hospital. This fact indicates that physicians are not missing oculoglandular tularemia and calling it Parinaud's conjunctivitis, and it refutes statements that the two diseases are one.

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Abstracts from Current Literature

EDITED BY DR. WILLIAM ZENTMAYER

Bacteriology and Serology

THE ANTIBACTERIAL ACTION OF TEARS ON STAPHYLOCOCCI. R. THOMPSON and E. GALLARDO, Am. J. Ophth. **24:** 635 (June) 1941.

Thompson and Gallardo give the following summary:

"An inhibiting action of tears against staphylococci was clearly demonstrated. Fifty-percent concentrations of the tears in broth inhibited the growth of 15 of 16 orange, mannitol-fermenting, coagulase-producing staphylococci, but these organisms grew well in 25-percent tear concentrations. All of 25 white, non-mannitol-fermenting, non-coagulase-producing staphylococci were inhibited by 50-percent tear concentrations; a number of the white strains were inhibited by 25-percent tear concentrations.

"The action of tears against the staphylococci was not due to lysozyme, since heated, acidified tears lost all trace of anti-staphylococcal action, although the lysozyme content was unaffected by the heating."

W. S. REESE.

Congenital Anomalies

PARTIAL COLOBOMA OF THE SCLERAL-LIMBUS ZONE WITH VISIBLE SCHLEMM'S CANAL. K. W. ASCHER, Am. J. Ophth. **24:** 615 (June) 1941.

Ascher gives the following summary of his paper:

"The occurrence of embryotoxon posterius corneae is not so rare as one would infer from the paucity of present-day literature on the subject.

"In a group of 167 cases in Alabama, 3 embryotoxa were found.

"Heredity is responsible in the type of case showing a partially visible Schlemm's canal.

"A case of bilateral nasal embryotoxon (type II, Bloch), and unilateral partial congenital defect (coloboma) of the scleral-limbus zone is described.

"Because of this defect, the transparent corneal tissue extends farther peripherally than usual, and in this region was observed a hitherto undescribed dark vessellike formation, corresponding in size, shape, and location to a part of the canal of Schlemm.

"This is the first and only case that has been described in which a part of Schlemm's canal seemed to be visible and accessible from the exterior of the eye."

W. S. REESE.

Cornea and Sclera

HISTOLOGIC CHANGES BY WHICH THE DISTURBANCE OF CORNEAL SENSITIVITY IN HERPES MAY BE EXPLAINED. K. A. REISER, Klin. Monatsbl. f. Augenh. **104:** 257 (March) 1940.

Observation on histologic specimens from rabbits led Reiser to the opinion that the virus in herpetic keratitis after inoculation shows no predilection for the nervous apparatus of the cornea. Lesions of the corneal nerves occur in the late stage of herpes, long after a disturbance in corneal sensitivity exists. Looking for the cause of this disturbance, Reiser turned his attention to the leukocytes. He found them longitudinally deformed and arranged in straight rows, forming lattices in cases of dense infiltration. The neural terminal reticulum, the elastic and collagenous fibers of the connective tissue and the lymph spaces were twisted into a regular latticework. The structural system of the cornea was outlined by rows of leukocytes which immigrated into the tissues at the onset of herpetic keratitis. Thus the leukocytes get in contact with the finest nerve elements at that early stage, exposing them to chemical and mechanical lesions. The micro-organisms which cause other forms of keratitis (e. g. vaccination keratitis and serpent ulcer) create latticed infiltrations but no damaging effect on the nerve tissue. The causative organisms of these two diseases remain near the focus of infection. Those of herpetic keratitis, on the other hand, are movable and easily transportable elements. They cause new foci anywhere in the cornea before the original herpetic foci can be reached by the leukocytes. In vaccination keratitis a single defensive reaction takes place in the form of creation of a wall of lymphocytes. In herpetic keratitis an extensive and always diffused infiltration occurs. This infiltration involves the finest intracorneal nerve elements, subjecting them to toxic and mechanical lesions much more extensive than those in other forms of keratitis. In herpes corneae, furthermore, an abundance of extravascular leukocytes is found in the tissues of the corneal margin. The so-called radial nerve branches entering the cornea are surrounded by a sheath of leukocytes for some distance. The soft perineural tissue appears to offer a favorable passageway for the leukocytes to enter the corneal parenchyma. The sensitive conduction from the cornea to the central nervous system is blocked at the limbus by the inflammatory changes. Pain frequently attributed to ciliary neuralgia may be explained by these changes at the limbus.

Several histologic factors bring about the disturbance of sensitivity in corneal herpes: (1) infiltration more extensive and diffused than that of other forms of keratitis, (2) active inflammatory changes surrounding the nerves, especially in the area of the limbus, and (3) changes in the larger intracorneal nerve bundles occurring during the later stages. The involvement of the nerve bundles is brought about by the anatomic conditions in the perineural tissue and by the morphologic peculiarities of the corneal parenchyma.

K. L. STOLL.

Experimental Pathology

EXPERIMENTAL ACUTE IRIDOCYCLITIS IN RABBITS PRODUCED BY COLIFORM BACTERIA ISOLATED FROM THE UPPER RESPIRATORY TRACT OF MAN. C. BERENS and E. L. NILSON, Am. J. Ophth. **24:** 645 (June) 1941.

Berens and Nilson give the following summary and conclusions:

"1. Using coliform bacilli found in the upper respiratory tract of man, transitory acute iridocyclitis was produced in rabbits with smaller amounts of culture and in a higher proportion of animals than when other types of bacteria, ordinarily found in the same tract, were used.

"2. Iridocyclitis was also produced by filtrates of these cultures. This suggests that the inflammation may be caused by a filterable factor rather than by the accumulation of bacteria within the blood vessels of the iris.

"3. The iridocyclitis-producing power and toxic effects of both filtrates and cultures were found to diminish with age.

"4. It was possible to produce a temporary partial or complete immunity to the coliform bacilli in rabbits by one or more intravenous injections of small doses of culture or filtrate.

"5. Filtrates prepared from the iridocyclitis-producing strains of coliform bacilli produced the same intensity of iridocyclitis as did the cultures from which they were prepared, when injected into rabbits in similar amounts.

"6. The upper-respiratory coliform bacteria used in these experiments were more lethal and produced a more severe iridocyclitis in rabbits than did miscellaneous fecal coliform strains.

"7. The apparent high incidence of coliform bacteria obtained from the upper respiratory tract of patients with eye diseases, and the ability of these strains to produce acute iridocyclitis in rabbits, seem to warrant further study of the possible role played by these organisms in the etiology of eye diseases, supposedly caused by focal infection."

W. S. REESE.

General Diseases

LATENT OCULAR TUBERCULOSIS. C. CHARLIN, Arch. de oftal. de Buenos Aires **15:** 489 (Oct.) 1940.

This is a chapter of Charlin's "Clinical Lessons on Ophthalmic Medicine."

Two cases are here reported. One was a case of parenchymatous keratitis of tuberculous origin treated off and on for ten years by Charlin and others as of syphilitic origin, the indications of its tuberculous nature being overlooked. After a few relapses the patient improved with tuberculin therapy. The other was a case of uveitis of two months' duration in which the diagnosis of its tuberculous nature was not at first apparent; in this case, also, improvement was obtained from tuberculin.

Charlin discusses latent ocular tuberculosis and stresses the necessity of paying more attention to the general condition of the patient

(facies, appetite, digestive functions, sleep, body weight and menstruation), especially when the nature of the disease is not clear; to recurrences, and to special examinations for tuberculous lesions elsewhere than in the eye.

The author distinguishes two types of ocular tuberculosis: a follicular type, with the follicles taking the form of miliary infiltrations or coalescing to constitute a confluent variety, and a nonfollicular, or non-nodular, form, which is less easy to distinguish clinically, since similar lesions have a different causation, and which constitutes the majority of the latent infections referred to.

The only certain proof is the reaction to tuberculin treatment, the Mantoux test not being reliable.

C. E. FINLAY.

Glaucoma

INTRAVENOUS INJECTION OF HYPERTONIC SOLUTION OF SODIUM CHLORIDE AND INTRAOCULAR TENSION. G. F. COSMETATOS, Klin. Monatsbl. f. Augenh. **104:** 549 (May) 1940.

The author used intravenous injections of hypertonic solutions of sodium chloride experimentally in the treatment of glaucoma and intoxication with quinine. The experiments were prompted by the research of S. Dontas, who obtained good results with this method in epilepsy, schizophrenia and Parkinson's disease, by what he called shifting of the osmotic balance between blood and tissues. The result was the voiding of water from the tissues into the blood, coupled with dilation of the blood vessels. Since reduction of the water content of the tissues produced a reduction of the irritability of the nerve cells, a quieting effect on the brain function was produced by the injections. The injections, on the other hand, may irritate the ganglion cells, as proved in some cases of melancholia. Experiments on dogs showed a decrease of the intraocular tension about one hour after intravenous injection of 200 cc. of a 5 per cent solution of sodium chloride. The drop amounted to from 25 to 5 mm. of mercury measured with the Schiøtz tonometer. Similar results were obtained in human beings.

The author concludes that these injections may reduce the intraocular tension in glaucoma even without the use of pilocarpine. They produce contraction of the pupil in normal eyes and reduction of the intraocular tension lasting as long as the pupil remains contracted. The injections are indicated in the treatment of patients who require a decompressing operation on an eye in which the tension is very high and on which pilocarpine has failed to act. Glaucoma which responds to this treatment may be due to edema of the vitreous, with retention of water in the other tissues of the eye.

The opinions of other authors are cited. Solutions of from 10 to 30 per cent were recommended. The author employed intravenous injections of 250 cc. of a 5 per cent solution of sodium chloride in the treatment of simple chronic glaucoma. Pilocarpine was used locally in the treatment of absolute glaucoma. No result was obtained in secondary glaucoma with the pupil dilated by peripheral synechias. The result was prompt in every case of secondary glaucoma with narrow pupil.

K. L. STOLL.

Injuries

TRAUMATIC LESION OF THE CORNEA. VILA ORTIZ, Arch. de oftal. de Buenos Aires **16:** 19 (Jan.); 70 (Feb.); 130 (March); 180 (April) 1941.

This is a lengthy paper appearing in four numbers of the archives, dealing with the relation of corneal injury to incapacity for work, its medicolegal evaluation and clinical and theraputic considerations.

After calling attention to the vulnerability of the cornea to trauma, upheld by statistical data from different countries, Vila Ortiz presents his own experience. Corneal lesions constitute 59.2 per cent of all ocular traumatisms. As regards age, he finds that 62.3 per cent occurred in workers under 30 and 37.7 per cent in persons over that age and points to the medicolegal importance of this ratio, due, on the one hand to the greater indemnity for injuries to minors and, on the other, to the professional inability of the aged maintained by some authors.

Of the persons affected, 94.7 per cent were males. Of the injuries, 51 per cent occurred in the left eye and 45.37 per cent in the right. The author classifies the lesions as follows: contusions, 9.5 per cent; perforating lesions, 7.5 per cent, and nonperforating lesions 11.1 per cent; penetration by a foreign body, 55.9 per cent; chemical burns, 6.9 per cent; thermic burns, 3.9 per cent, and rare lesions, 4.9 per cent.

Vila Ortiz next takes up in detail each of the different varieties, with a review of the literature—the different aspects they may present, the inflammatory complications which are apt to develop, the sequelae and the degree of incapacity which may result.

A discussion of the prevention of such injuries follows, the defects in existing legislation being stressed. Medicolegal evaluation of the resulting incapacity due to loss of vision is then discussed, the Argentine, the French and the German incapacity tables compared and conclusions and recommendations made.

C. E. FINLAY.

TWO CASES OF OCULAR TRAUMATISM. A. CARDENAS, Arch. de oftal. de Buenos Aires **16:** 453 (Aug.) 1941.

Two cases of unusual ocular trauma are reported.

In the first, a woman in a lunatic asylum attempted to gouge out both eyes of a fellow inmate. The left eye was luxated in front of the lids, with rupture of the lower portion of the conjunctiva and of the interior and the internal rectus muscle. The right eye was exophthalmic, with imperfect closure of the lids, and the lower portion of the conjunctiva was torn and the inferior rectus muscle severed. Both corneas showed multiple erosions. In the right eye cellulitis followed panophthalmitis from an infected corneal ulcer. The left eye finally presented a corneal leukoma, not involving the pupillary area, and complete symblepharon between globe and lower lid.

The second case was of circular iridodialysis from a contusion with a hammer. This iris was extracted with a forceps. Healing was normal, with a resulting visual acuity of 2/3. There was a high degree of photophobia.

C. E. FINLAY.

Lacrimal Apparatus

BOECK'S SARCOID OF THE LACRIMAL GLAND. H. R. SNIDERMAN, Am. J. Ophth. **24:** 675 (June) 1941.

Sniderman gives the following summary:

"A brief review of cases of ocular sarcoid is reported along with a new syndrome of bilateral involvement of the lacrimal glands with concomitant bilateral iridocyclitis. The diagnosis was made by biopsy of the lacrimal gland and typical chest X-ray changes. The treatment was not extraordinary except for X-ray therapy to the lacrimal gland, to which there was a good response."

W. S. REESE.

Lens

AN ATTEMPT TO PRODUCE DINITROPHENOL CATARACTS IN HYPOTHYROID RATS. G. K. SMELSER, Am. J. Ophth. **24:** 680 (June) 1941.

Smelser reports a series of experiments in which dinitrophenol was given to thyroidectomized rats. He confirmed previous reports that administration of dinitrophenol to laboratory animals does not result in cataract and extended his studies to include animals with hypothyroidism.

W. S. REESE.

DOYNE'S DISCOID CATARACT (COPPOCK). P. H. ADAMS, Brit. J. Ophth. **26:** 152 (April) 1942.

Pursuant of many inquiries as to the appearance of Doyne's discoid cataract (Coppock) under the slit lamp, Adams describes the appearance of the opacity of a member of the original family, first reported on by Nettleship and Ogilvie: ". . . the disc is seen to be a small spotted biconvex opacity, the spots looking bright white in the beam of the lamp, with a more or less clear central area. The Y's could not be definitely identified but the opacity appeared to involve the embryonic nucleus only, and to be of the nature of a very small 'lamellar' cataract.

"In the case illustrated here, there is a large vacuole at about XI o'clock on the edge of the opacity. This is a senile change which has developed fairly recently."

W. ZENTMAYER.

Lids

HESS OPERATION FOR PTOSIS. R. F. PEREIRA, Arch. de oftal. de Buenos Aires **16:** 241 (May) 1941.

To avoid corneal injury from lagophthalmos due to the usual occlusive bandage used after the Hess operation, which is the operation of choice for ptosis in the Arganaz clinic, Pereira applies a celluloid shell, the edges of which are hermetically sealed with adhesive plaster. This can be kept in place for weeks, allowing constant inspection of the eye, and is removed only when necessary for cleansing purposes.

C. E. FINLAY.

Methods of Examination

TESTING NIGHT VISION. N. B. HARMAN, Brit. M. J. **1:** 636 (April 26) 1941.

Dr. W. D. Wright, a lecturer in physics, has written a small seven page booklet called "Test for Night Vision" which accompanies a test apparatus designed by him. This apparatus consists of a baseboard measuring 8 by 6 inches (20 by 15 cm.) on which are hinged two boards which will stand upright. One is a support for the test cards; the other, on the side away from the patient's eyes, has a disk 1 inch (2.5 cm.) in diameter covered with a luminous radium compound which gives a faint glow of light that serves to illuminate the test cards. These test cards are black. On each is one letter, a capital C, $4\frac{3}{16}$ inches (11 cm.) in diameter and $\frac{5}{8}$ inch (1.6 cm.) in breadth. These letters are of nine shades varying from pure white to a dark gray that is almost black. The patients to be tested should remain in the dark for fifteen minutes. Then the cards are exposed to the radium glow and examined at a distance of 12 inches (30 cm.). The test lies in the ability to see the gap in the circle of the C.

Harman suggests the following criticisms: The radium illumination may be variable, the hands of the examiner when shifting the cards are disturbing to the examinee and the examination of the more difficult cards is hindered by the sheen of the smooth black cards and the baseboard. The test is made at 12 inches, whereas long experience has shown that any standard test of vision should not be at a distance of less than 5 to 6 meters.

Some years ago Harman described a method of testing the light sense in patients suspected of having tobacco amblyopia (*Lancet* **2:** 821, 1904). He has also tried other tests. The aim has been to use a standard illumination and a test that would need a minimum of visual acuity. A standard candle, that is one burning 120 grains (8 Gm.) in an hour, is easily got, and it does not vary. This candle is fitted inside a box somewhat like a child's toy magic lantern but with no lenses, a wider snout and the inside painted dull black. This will furnish a standard beam of light which will illuminate with a glow the usual Snellen test card from a distance. Since the Snellen letters require both sight and knowledge of letters, Harman uses a revolving E test. When in a dark room the boxed-in candle light is placed alongside the patient at a distance of 5 meters from the E test card; the light on the card is only $\frac{1}{269}$ foot candle. Yet a normal-sighted person in the early thirties who could see 5/5 easily with a normally lighted test card could see with the candle glow 5/20 and occasionally 5/15. In the tests it was observed that one can get better vision by looking a little away from the test card; it is well known that the light sense of the retina away from the macula is better than at the macula.

Harman's latest distance test card is still simpler and requires a minimum of form sense and therefore relies almost wholly on the light sense. The 5 meter distance test card is a board 1 foot (33 cm.) square. This is covered with black velvet. The test objects are white disks $\frac{1}{2}$ inch (1.3 cm.) in diameter arranged in groups of from four to seven on the velvet, each disk being $\frac{1}{8}$ inch (0.3 cm.) from the others. These groups are covered by another partition with a 3 inch (7.6 cm.) hole.

The candle box is fitted at 5 meters from the test card. The room is dark except for the candle rays. The patient stands beside the candle box and looks toward the test card. The object is to find the maximum distance at which the patient can both see and count the separate white spots.

Experience has shown that variations in night vision do not depend entirely on the light sense. Many other factors diminish night vision or vary it. Chief among these are the size of the pupil, the condition of the crystalline lens and the retinal integrity. ARNOLD KNAPP.

Neurology

THE WERNICKE SYNDROME. N. JOLLIFFE, H. WORTIS and H. D. FEIN, Arch. Neurol. & Psychiat. **46:** 569 (Oct.) 1941.

The authors review the literature as to the occurrence of Wernicke's hemorrhagic polioencephalitis in alcoholic and in nonalcoholic persons, discussing the probability of the causative agent being not a toxin, such as alcohol, but instead a vitamin deficiency. This probability is supported by the fact that a similar pathologic picture has been experimentally reproduced in thiamine-deficient animals (dogs, pigeons and rats).

They analyze 27 cases of Wernicke's syndrome (in 3 of which the syndrome occurred in nonalcoholic persons), and among the conclusions reached are the following of special ophthalmologic interest:

"The syndrome as originally described by Wernicke is probably a combination of several nutritional deficiencies affecting the nervous system and need not necessarily be complete in any case. It is of course possible that the exact syndrome which Alexander has reproduced experimentally in pigeons may on occasion occur in uncomplicated fashion in man, but except for ophthalmoplegia, the other symptoms would be difficult to evaluate from a purely clinicopathologic point of view.

"Our results indicate that (*a*) the ophthalmoplegia is a thiamine deficiency, (*b*) the clouding of consciousness may be related to anything which interferes with proper cerebral metabolism, some of the known offenders being lack of carbohydrate, lack of oxygen, lack of thiamine or nicotinic acid or riboflavin or of all three and probably a lack of many other substances now under investigation, and (*c*) the ataxia is difficult to evaluate and its response to therapy has not as yet been worked out. . . .

"The ophthalmoplegia is invariably preceded or accompanied by peripheral neuropathy. This tends to confirm Alexander's thesis that smaller amounts of thiamine are necessary to prevent the polioencephalopathic changes than are necessary for antineuritic action. . . ."

R. IRVINE.

HETERONYMOUS HEMIANOPSIA AND INTRACRANIAL TUMORS IN THE NEIGHBORHOOD OF THE CHIASMA. R. ARGAÑARAZ, Arch. de oftal. de Buenos Aires **16:** 349 (July) 1941.

Argañaraz classifies tumors in the neighborhood of the chiasma into intrasellar (hypophysial adenomas and craniopharyngiomas) and extra-

sellar, or parachiasmatic (meningiomas, aneurysms and other vascular forms and arachnoiditis) tumors.

In the case of hypophysial adenomas, the endocrine and sexual disturbances precede the visual. The visual changes, however, appear early, in the shape of bitemporal hemianopsia, first noticeable in the upper and external quadrants. This progresses gradually, according to the density of the diaphragma sellae. When the tumor develops irregularly forward, blindness of one eye with optic nerve atrophy and temporal hemianopsia of the other eye usually results. If it develops backward, it can destroy an optic tract, with the production of homonymous hemianopsia. Only when it becomes large can papilledema and symptoms of cranial hypertension result.

A craniopharyngioma is a congenital lesion originating in congenital remains of Rathke's pouch. It usually acquires an extraordinary development at puberty, which coincides with the sexual development. In roengenograms, alterations in the shape of the sella are as a rule clearly discernible. The visual field changes vary according to the direction of growth.

Meningiomas comprise 16 per cent of cerebral tumors, a high proportion involving the meninges covering the optic nerves, chiasma and optic tracts. They are always parasellar and unaccompanied by any deformity of the sella. Visual symptoms appear early and vary according to the site of the lesion. Secondary disturbances of pituitary function may be present. The tumor may be situated in the olfactory fossa and may affect the chiasma from above, with vascular lesions leading to binasal hemianopsia, the disturbance being most pronounced in the inferior quadrants. As a late manifestation, one may find the Foster Kennedy syndrome, and early unilateral anosmia is the rule.

The anterior tubercle of the sella is a frequent site. The hemianopsia is usually bilateral, with an early involvement of the upper and outer quadrants, and gradual extension to the lower quadrants. The small wing of the sphenoid bone is another frequent site. The visual field disturbances may appear early or late, with signs of compression of the structures passing through the superior sphenoidal fissure. The intracanalicular portion of the optic nerve may be involved, the lesion extending forward into the orbit and backward into the cranium. Roentgenograms of the optic foramen facilitate the diagnosis; the orbital symptoms are apt to be more pronounced. The involvement of the optic nerve sheath leads to the development of a tumor formerly called myzoma.

Aneurysms and vascular lesions in the neighborhood of the chiasma may affect the chiasms secondarily. The visual field changes vary according to the site of the compression.

Arachnoiditis situated at the cisterna magna may affect the chiasma secondarily, with symptoms similar to those of the meningiomas.

In the diagnosis of these tumors, the visual field and the fundus changes must be considered, together with the patient's age, endocrine disturbances and sexual history and the results of roentgen examination of the shape of the sella. Ventriculography often facilitates the determination of the size and localization of the tumor.

As to treatment, Argañaraz advises that preliminary roentgen irradiation should precede any surgical procedure. The selection of a

transfrontal or intrasphenoidal approach depends on the circumstances. There is a mortality of 5 per cent for the former and of 7.2 per cent for the latter. The mortality for meningiomas is 14 per cent.

C. E. FINLAY.

Ocular Muscles

SURGICAL TREATMENT OF FUNCTIONAL STRABISMUS. J. SVERDLICK, Arch. de oftal. de Buenos Aires **15:** 246 (May) 1940.

The author attributes the actual perfection of the surgical treatment of functional strabismus to the improvement in knowledge of neuromyology. The operations per se, as well as the preorthoptic treatment and the following orthoptic training, only constitute stages in the sensorimotor coordinative treatment of strabismus, a combination leading to the attainment of the full benefit to the patient by a realization of the therapeutic equation cosmetic result plus reestablishment of binocular vision.

Surgical intervention is indicated when preorthoptic treatment and orthoptic training have failed to correct the deviation or other factors, such as a psychic handicap and economic difficulties.

Sverdlick reduces the various operative technics to those of lengthening the muscle by (*a*) tenotomy or (*b*) recession and those of shortening the muscle by (*a*) advancement with or without resection and (*b*) tucking.

Simple tenotomy owes its popularity to its extreme facility, which is more than counterbalanced by its multiple disadvantages from lack of accuracy and cosmetic results. After mentioning the general objectives, requirements and technic of the other procedures, the author takes up the question of the most appropriate age for operation. He is opposed to all operations before the age of 6 years, preferring the age from 8 to 10. Prior to this period, preorthoptic treatment and orthoptic training conducive to the prevention of amblyopia, loss of central fixation and development of an anomalous retinal correspondence should be carried out.

The choice of the operative procedure should be subordinated to the physiopathologic conditions present and to a study of the patient's visual function, recession being indicated when there is an excess of divergence or an excess of convergence with hyperkinesis of the internal rectus muscle and advancement when there is a lack of divergence or an insufficiency of convergence with hypokinesis of the internal or the external rectus muscle. The results depend not only on the method chosen but on the ability of the surgeon. The author prefers operating by successive stages.

C. E. FINLAY.

Operations

OCULOPALPEBRAL PROSTHESIS. C S. DAMEL and O. TAULLARD, Arch. de oftal. de Buenos Aires **16:** 336 (June) 1941.

A case is reported in which there was total exenteration of the orbital contents, with complete abscission of the lids and surrounding soft parts, followed by epidermization of the resulting cavity. After

accurate molding, a structure of light dental plate material was made to fill up the existing cavity. On its anterior surface was fixed an artificial eye, with lids, cilia and eyebrows of a light plastic material, the whole being attached to a spectacle frame. Photographs of the final satisfactory prothesis are included. C. E. FINLAY.

Orbit, Eyeball and Accessory Sinuses

PSAMMOMA OF THE ORBIT. W. E. FRY and P. DELONG, Am. J. Ophth. **24:** 664 (June) 1941.

A brief clinical report is given of a case of psammoma of the orbit removed through an incision for a radical frontal-sinus operation. The pathologic changes are described and such tumors discussed, especially from the standpoint of nomenclature and origin. W. S. REESE.

INFECTIOUS ORBITAL PROCESSES. E. J. J. LAGOS, B. JUST TISCORNIA and A. RIVA, Arch. de oftal. de Buenos Aires **15:** 213 (May); 265 (June) 1940.

This is a lengthy and detailed study of infectious orbital processes, preceded by an accurate and minute anatomic description of the orbit and its contents, with special stress on its relations to surrounding cavities and structures and the development of these at different ages. The infections are studied from the point of view of their possible exogenous and endogenous origins, and separate descriptions are allotted to panophthalmitis, orbital peristitis, syphilitic and tuberculous osteomyelitis, orbital cellulitis, tenonitis, orbital abscess, thrombophlebitis of the cavernous sinus, parasitic infections of the orbit and metastatic infection. There are 44 case histories and a rich bibliography.

C. E. FINLAY.

Retina and Optic Nerve

TOXIC OPTIC NEURITIS FROM ACETYLARSAN. A. VÁZQUEZ-BARRIÈRE and I. ERREA, Arch. de oftal. de Buenos Aires **15:** 504 (Oct.) 1940.

Although acetylarsan (p-oxyacetylaminophenylarsinate of diethylamine) is considered one of the least dangerous of the pentavalent arsenicals if the proper precautions are taken, a case is here reported in which, notwithstanding the absence of recognized contraindications and the fact that the dosage was according to accepted tenets, a reduction in vision was noticed three hours after the second injection.

The patient, a woman 73 years of age, suffered from headaches and dizziness. There was a positive Wassermann reaction; treatment with bismuth and arsenic was without success. There was no renal or hepatic insufficiency; the cardiovascular system was in good condition; the patellar, heel and pupillary reflexes were normal; there was no Romberg sign and no motor or sensory disturbances.

The ocular lesion took the shape of numerous punctate retinal hemorrhages around the disk, with reduction of vision to counting of fingers at 1 meter and concentric contraction of the visual fields.

The use of acetylcholine and of sodium thiosulfate was followed by a slight temporary improvement in visual acuity but not in the visual fields.

C. E. FINLAY.

DISCIFORM DEGENERATION OF THE MACULA. C. S. DAMEL, J. A. GALLINO and O. A. TRAVI, Arch. de oftal. de Buenos Aires **16:** 376 (July) 1941.

After a detailed review of the extensive literature and of the variations in the nomenclature, the authors conclude that the pathologic changes and the clinical symptoms point toward an angiopathic choroidal lesion with special involvement of the choriocapillaris. They report 3 cases and reproduce retinographs showing the disease at different stages of development.

C. E. FINLAY.

Uvea

ALBUMINOMETRY AND CYTOLOGY OF AQUEOUS HUMOR IN IRIDOCYCLITIS. C. ESPILDORA LUQUE and F. TSCHUMI TRAUTVETTER, Arch. de oftal. de Buenos Aires **15:** 159 (April) 1940.

After pointing out the difficulty in many instances of determining the etiologic factor in iridocyclitis, the authors suggest chemical and cytologic examination of the aqueous humor as a guide and present results of their investigations, with preliminary conclusions.

Their experiments comprised three series: (1) study of 21 rabbits with the objective of determining the proper technic; (2) study of 10 normal human eyes and (3) examination in cases of iridocyclitis.

In normal human eyes, the albumin content ranged from 0.1 to 0.3 Gm. per thousand cubic centimeters, with an average of 0.15 Gm. (Magitot and Mestrezat, 0.16 Gm.), with no cellular elements.

In 3 cases of exogenous iridocyclitis (complicating a serpiginous corneal ulcer, a penetrating corneal wound and an infection following and Elliot trephining) the albumin content was 14.5, 14 and 8 Gm. per thousand cubic centimeters, respectively, with numerous cells, 80 per cent being polymorphonuclear. In 2 cases of gonococcic iritis, the albumin content was 3.5 Gm. per thousand cubic centimeters, the polymorphonuclears ranging from 72 to 78 per cent, the lymphocytes from 16 to 20 per cent and the monocytes from 6 to 8 per cent. In 5 cases of tuberculous iridocyclitis, the albumin content ranged from 0.05 to 2 Gm. per thousand cubic centimeters, the polymorphonuclear cells from 26 to 40 per cent, the lymphocytes from 50 to 64 per cent and the monocytes from 2 to 10 per cent. In 4 cases of syphilitic iridocyclitis, the albumin content ranged from 8 to 8.5 Gm. per thousand cubic centimeters, the polymorphonuclear cells from 6 to 15 per cent, the lymphocytes from 75 to 90 per cent and the monocytes from 6 to 10 per cent.

The following conclusions are drawn:

1. The normal aqueous of the rabbit has an albumin content of from 0.18 to 0.22 Gm. per thousand cubic centimeters and no cellular elements.

2. The albumin content of the human aqueous is 0.15 Gm. per thousand cubic centimeters (average), with no cellular elements.

3. Puncture of the anterior chamber and aspiration of the aqueous humor are usually innocuous; in cases of tuberculous iridocyclitis they may be beneficial.

4. Exogenous iridocyclitis is characterized by an enormous rise in the albumin content (8 to 14 Gm. per thousand cubic centimeters) and a frank increase in polymorphonuclear cells.

5. Gonococcic iridocyclitis is also accompanied with an increase in polymorphonuclear cells, but the albumin content does not rise over 4 Gm. per thousand cubic centimeters.

6. In tuberculous iridocyclitis, the proportion between polymorphonuclear leukocytes and lymphocytes is equalized, but the albumin content did not rise over .2 Gm. per thousand cubic centimeters except in a case complicated with hypertension.

7. In syphilitic iridocyclitis, lymphocytes predominate, and the albumin content is somewhat higher than in tuberculous iridocyclitis.

C. E. FINLAY.

Society Transactions

EDITED BY DR. W. L. BENEDICT

PITTSBURGH OPHTHALMOLOGICAL SOCIETY

DR. J. C. MARKEL, *Presiding*

November 6, 1941

Excision of Conjunctival Papilloma and Mucous Membrane Graft. DR. E. J. WENAAS, Youngstown, Ohio.

A 67 year old mill worker was found to have a flat red-brown tumor of the bulbar conjunctiva involving the entire nasal portion of the conjunctiva to the caruncle from the midline above to 8 o'clock below. The cornea was infiltrated for 3 mm. Biomicrospy revealed a lobulated tumor with a rosette formation and numerous loops of blood vessels. The blood supply to the tumor was not separate. The biopsy report indicated probably potentially malignant squamous cell papilloma of the conjunctiva.

The tumor was excised during local anesthesia, the excision including a 2 mm. extension into normal conjunctiva. No scleral adhesions were found. The infiltrated portion of the cornea was excised with a cataract knife and cauterized with electric current.

A mucous membrane graft was obtained from the inner part of the lower lip, thinned, fashioned and secured by interrupted fine silk sutures into the defect. The corneal defect was covered as in a flap. The sutures were removed on the sixth day, and healing was uneventful. After two weeks the excess graft was trimmed down to the corneal scar. The vision was 20/40. There was no recurrence after five months. The graft amounted to almost one half of the bulbar conjunctiva.

DISCUSSION

DR. EDWARD STIEREN: Dr. Wenaas is to be congratulated on such a smooth result of a large graft. I usually prefer to use several smaller grafts. A papilloma must be removed thoroughly or it will recur, and do so rapidly, and may become malignant. Absence of melanin usually indicates that the tumor is benign. I have removed a large tumor with simple cautery with a good recovery.

DR. E. J. WENAAS, Youngstown, Ohio: It has been pointed out by Dr. Spaeth that if the cornea is involved the possibility of malignancy is greater, so that indication for complete removal of the tumor was all the more obvious.

Hole at the Macula: Report of Four Cases with Photographs of the Fundi. DR. CHARLES F. KUTSCHER and DR. GEORGE H. SHUMAN.

Photographs in color illustrating 4 cases of hole at the macula were presented. In 3 of the cases the hole was the result of a severe blow

on the anterior part of the eye and displayed the typical appearance of a sharply defined, slightly depressed, deep red disk occupying the macular region. In the fourth case the hole was nontraumatic and the patient a man aged 47. The precursory lesion had been observed in August 1934, seven years before the photograph of the hole was taken. The initial lesion was a retinal hemorrhage measuring about 2 disk diameters and overlying the macular region. General examination disclosed badly infected tonsils and teeth with apical abscesses. About one month after the first observation, the hemorrhage having partly cleared, a sharply outlined, pale, blue-gray circular mound about ¼ disk diameter in size was found in the center of the hemorrhagic area. The macular hole photographed in August 1941 was devoid of the finely granular, deep red choroidal base seen in the other 3 cases. Instead, the whitish reflex of the sclera was plainly seen and there was a heavily pigmented taglike border at the superior nasal portion of the hole. The nerve head and other parts of the fundus appeared entirely normal. The fellow eye remained normal in structure and function from the first. In view of the development of this typical macular hole, which was a settled lesion unaccompanied by the appearance of any other pathologic change in the fundus or other parts of the eye during seven years, a retrospective diagnosis was made of cystic degeneration of the macula due to foci of infection found in the tonsils and teeth, followed by formation of a hole in the retina and pressure atrophy of the choroid at the site of the lesion.

DISCUSSION

DR. WADE CARSON: I saw the last patient seven years ago and am interested to see the change.

DR. EDWARD STIEREN: Macular hemorrhages often produce a hole at the macula. At times they may be seen only with a binocular ophthalmoscope.

DR. CHARLES KUTSCHER: Binocular ophthalmoscopic examination is important. In a patient seen recently, a cyst of the retina was observed under binocular ophthalmoscopic examination to project into the vitreous, whereas it had been missed by observation with other instruments.

NEW YORK ACADEMY OF MEDICINE, SECTION ON OPHTHALMOLOGY

KAUFMAN SCHLIVEK, M.D., *Chairman*
BRITTAIN PAYNE, M.D., *Secretary*

February 16, 1942

Recession of the Trochlea in Overaction of the Superior Oblique Muscle. DR. DONALD W. BOGART.

The case presented is one of cyclotropia with hypotropia in which operation was performed and the condition was definitely improved. The success attained by Dr. Wendell L. Hughes in a similar case with

an operation to be described, which he devised, suggested a similar procedure in my case.

Miss E. S., aged 26, presented right hypotropia of 4 to 6 prism diopters and cyclotropia of 12 prism diopters with the head in the upright position. Her vision was normal, and refraction showed a moderate simple hyperopic astigmatism with the rule. The diagnosis was spasm of the right superior oblique muscle.

Her chief complaint was extreme fatigue and eyestrain after even short periods of use of her eyes. Fusion was possible momentarily with the head tilted down and to the right. The operation was performed as follows:

A 2 per cent solution of procaine hydrochloride with a few minims of epinephrine hydrochloride solution was injected deeply enough to anesthetize the skin, the periosteum and the region about the trochlea. An incision was made through the skin and superficial fascia parallel to the orbital rim and over the trochlea, so that the periosteum over the orbital rim was exposed. The periosteum was incised and undermined with a periosteal elevator along the roof of the orbit 2.5 cm. back from the rim. Parallel incisions 0.5 cm. long and 1 cm. apart were made through the periorbita on each side of the trochlea. The periorbita with the trochlea was pushed backward. The muscle and the skin were closed in layers, and a small plug of gauze was placed over the area operated on. A pressure dressing was then applied to maintain the retroplacement of the trochlea. The dressing and the sutures were removed in four days, and a similar pressure dressing was applied for another four days and then removed. The exact amounts of retroplacement cannot be given at this time owing to the fact that sufficient cases have not been recorded.

Postoperatively, the patient followed for ten months reported complete comfort for the first time in years and was able to carry on normal secretarial work. The right hypotropia was reduced to 3 prism diopters and the cyclotropia to about 3 to 4 degrees.

DISCUSSION

Dr. Wendell L. Hughes: This procedure was followed first in 1936 on a boy 16 years of age who had had a persistent head tilt. The vision was 20/20 in each eye, and there was fusion in the field of action of all the muscles except in the lower left field, in which there was diplopia with the right image below the left. The diplopia was variable owing to spasm of the superior oblique muscle. I felt that no other muscle was involved and that the ideal operation would reduce the effect of the superior oblique muscle. Not knowing of any procedure that had been done for that purpose, I decided on a retroplacement of the trochlea or a retroplacement of the periosteum with the trochlea. The final result was fusion throughout the field, except for a small amount of diplopia when the patient looked to the left, and correction of the head tilt.

A Case of Tumor of the Iris Root. Dr. H. M. Katzin.

A case was presented of malignant melanoma of the root of the iris in a man 40 years of age whose history was irrelevant and who had no ocular symptoms. The mass arose at the root of the iris and projected

into the anterior chamber at 8 o'clock, wrinkling the iris concentrically. During cycloplegia the pupil was eccentric, and slit lamp examination revealed the mass to be unevenly pigmented.

Microscopic sections after enucleation showed a minute tumor in the anterior portion of the root of the iris, occupying the whole thickness of the iris and invading the pectinate ligament, the region of Schlemm's canal and the ciliary body. In bleached specimens, the cells were seen to be remarkably uniform, epithelial in type and entirely lacking in mitotic figures or vascularity.

It was emphasized that if a biopsy iridectomy had been performed, the tissue would have appeared entirely benign, while the malignant process would have persisted, invading the pectinate ligament further.

DISCUSSION

Dr. Arnold Knapp: The diagnosis of tumor of the iris is often difficult, particularly in the differentiation between a benign and a malignant melanoma. The benign tumor has a characteristic brown color and is superficial. In this case, while the color was brown, the localization in the iris angle was unusual. In addition, there were furrows in the iris tissue concentric to the margin of the growth, which to my mind indicated that the tumor was deeply placed and consequently must be regarded as a malignant process.

Dr. Kaufman Schlivek: The diagnosis was not clear, and enucleation of the eye really required the encouragement of Dr. Knapp. Most of the ophthalmologists at the hospital advised against enucleation, but I favored removal. Many years ago Dr. Robert G. Reese had a similar case. The patient was first seen at my office, and enucleation was advised. After many ophthalmologists examined the patient, Dr. Reese performed an iridectomy slightly different from the usual procedure. The keratome section was made lateral to the tumor and was completed with the scissors; in this way tumor tissue was not disturbed. After six months a large mass invaded the vitreous body and enucleation was necessary. Had an iridectomy been done in this case, as Dr. Katzin mentioned, enucleation would finally have been necessary.

A Case of Lacerated Lid with Old Coloboma—Plastic Repair. Dr. Rudolf Aebli.

A case of traumatic coloboma extending through the entire height of the midportion of the left upper eyelid with a moderate loss of tissue and a 10 mm. separation was presented. The accident had been caused by a hook which caught under the upper lid and tore it upward. No injury to the eyeball was sustained. The lid was repaired by splitting both the nasal and the temporal part of the lid into two layers, excising the scar tissue and freeing cicatricial bands. The tarsal edges were sutured together with 0000 chromic catgut. An external canthotomy incision extending 2 mm. beyond the margin of the orbit was made and a second incision from this point upward. These incisions relieved the tension and permitted the tarsal edges to be brought into apposition. The skin edges were rarefied and sutured with silk in a different plane from the

tarsal sutures; the Wheeler halving procedure was employed at the lid margin. An excellent cosmetic result was obtained. The presentation was illustrated with lantern slides.

DISCUSSION

DR. WENDELL L. HUGHES: I think this type of procedure is important at the present time because it may be used more frequently in the near future. The coloboma was due to contraction of portions of the lid on each side of the laceration; there was no actual loss of tissue. In most such cases the defect can be corrected by the method Dr. Aebli described. Of course when there is a section of lid absent, a new problem arises, viz., to fill in the coloboma with tissue from elsewhere, either with tarsal tissue from the opposite lid or, as Dr. Aebli suggested, with cartilage, for example, cartilage from the ear. A free tarsal transplant from the opposite lid is probably the best. Nothing replaces normal lid tissue like normal lid tissue, and I think this principle, which Dr. Wheeler outlined, should be followed when possible.

Relation of Field Contraction to Blood Pressure in Chronic Primary Glaucoma. DR. ALGERNON B. REESE and DR. JOHN S. MCGAVIC (by invitation).

This article was published in full in the May issue of the ARCHIVES, page 845.

DISCUSSION

DR. ALGERNON B. REESE: We realize that in this work there are a number of sources of error which we did not know how to control. First, we found it impossible to determine the exact duration of the glaucoma. This is important, since an eye with a coefficient slightly below normal but with glaucoma of long duration may show the same percentage of retained field as one with a coefficient considerably subnormal but with glaucoma of shorter duration. Second, the great variability of the blood pressure and the intraocular pressure may have led to incorrect determinations. Third, it was impossible to determine the extent to which miotics had been used in the past. This was important in relation to the reading of the intraocular pressure. For instance, an eye may have had a mean intraocular pressure of 30 to 35 mm. of mercury for months or years before observation, but after the use of miotics the pressure may have ranged between 20 and 25. Before this eye was observed, the coefficient would have been lower than normal, but in our figures it may be represented as normal. In view of these sources of error, we are justified in saying only that our figures show a trend toward a better retention of field vision in patients with elevated blood pressure than in patients with normal or subnormal blood pressure. As a result of this investigation, I think we are justified in temporizing more with patients with glaucoma having increased vascular pressure than with those having normal or subnormal vascular pressure.

DR. ARNOLD KNAPP: I do not quite understand the purpose of this investigation. If it was to determine the prognosis after operation, the investigation should be instructive. After a number of years of experience

with glaucoma, one is impressed by how many persons keep their visual fields after the tension has been satisfactorily lowered; but there are a small number in whom, notwithstanding the fact that a satisfactory operation was performed, the visual fields continue to contract. I hope this is the group on whose condition the investigations of Dr. Reese and Dr. McGavic will throw some light.

Dr. Sigmund A. Agatston: This is an interesting study and to my mind has a definite basis. There is no question that the blood vessels are responsible for the condition of the optic nerve and the retina. If one thinks in terms of vessels in relation to function, one knows that in optic nerve atrophy secondary to papilledema or retrobulbar neuritis the disk with the better vessels always has better vision. I think Dr. Reese and Dr. McGavic are working on solid ground when they study the condition of the vessels, because that is what their reading means.

They say that when the blood pressure is high the visual field is retained. Why is it retained? Because when the blood pressure is high it is difficult to compress the arteries and to eliminate the normal circulation. In other words, circulation in the presence of increased intraocular pressure is better when the patient has a high blood pressure.

I have made that observation, but I did not go into it as Dr. Reese did. However, I did note that in patients with low blood pressure and increased intraocular tension the arteries are compressed to such an extent that one frequently thinks one is dealing with a hypertensive patient. If the patient has a high diastolic pressure, then the intraocular pressure has no effect on the arteries, and I think this explains why the visual field is retained. It is known that in retinitis pigmentosa, in which the visual fields are so definitely contracted, the blood vessels are so thin that sometimes they are hardly visible. In other words, the vision and the visual fields are in proportion to the size and the patency of the arteries.

Dr. John S. McGavic: In answer to Dr. Knapp's question, one purpose of this study was to try to explain the inconsistencies in the rate of contraction of the fields in different patients. We thought this might help us to determine the prognosis in future cases.

Virus Diseases of the Eye. Dr. Phillips Thygeson.

This article will be published in full, as an Ophthalmologic Review, in a later issue of the Archives.

DISCUSSION

Dr. Isadore Givner: This paper is an added tribute to the specialty of ophthalmology in pointing out its many-sided relations to highly scientific and even philosophic knowledge.

In the past decade, thirty-five infections of man have been proved to be due to viruses—almost as many as are known to be caused by bacteria. A long way toward the control of bacterial diseases has been traveled, and a good start has been made with the viruses.

Dr. Thygeson has covered the special technics devised for determination of the size and the chemical constitution. Among many of the

difficulties encountered in the study of viruses, I should like to emphasize two: First, the simple presence of specific antibodies does not necessarily indicate that the corresponding virus has caused an observed infection. Thus injections of typhoid bacilli into rabbits apparently normal but actually latently infected with virus III may lead to the production of antibodies for virus III as well as for the typhoid bacillus. Second, a negative response as far as growth on either the chorioallantosis or various tissue cultures in vivo or in vitro does not exclude the presence of a virus, for tissue and species specificity seems to be rather well developed for many of the viruses, and the best method for the detection of the particular virus may not as yet have been found.

News and Notes

EDITED BY DR. W. L. BENEDICT

SOCIETY NEWS

Reading Eye, Ear, Nose and Throat Society.—The thirteenth meeting of the Reading Eye, Ear, Nose and Throat Society, Reading, Pa., was addressed by Dr. Alfred Cowan, Sept. 16, 1942. Dr. Cowan is Professor of Ophthalmic Optics at the Graduate School of the University of Pennsylvania. The subject of his talk was "Interesting Aspects of Refraction." The society has made arrangements to attend in a body the meeting of the American Academy of Ophthalmology and Otolaryngology to be held Oct. 11 to 14, 1942.

American Academy of Ophthalmology.—At a meeting of the Council of the American Academy of Ophthalmology and Otolaryngology, held in Chicago on June 28, Dr. William L. Benedict was elected to the office of executive secretary-treasurer, to succeed the late Dr. William P. Wherry.

The forty-seventh annual meeting of the American Academy of Ophthalmology and Otolaryngology will be held at the Palmer House, Chicago, October 11 to 14, inclusive, under the presidency of Dr. Ralph I. Lloyd.

Obituaries

JOHN O. McREYNOLDS, M.D.

1865–1942

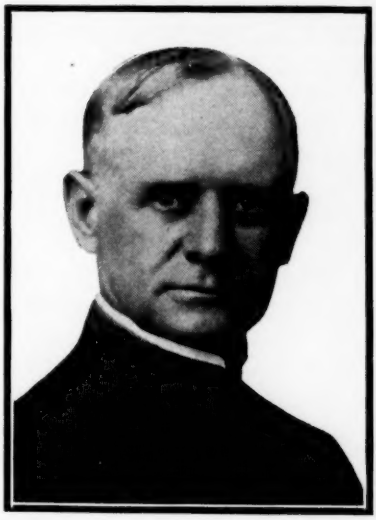
John O. McReynolds died at his home in Dallas, Texas, on July 7, 1942, aged 76. With his passing there closes another chapter in the book of pioneer American ophthalmologists, and the book is almost finished. He was born in Elkton, Ky., in 1865, the son of Richard McReynolds and Victoria Campbell Boone, members of prominent Virginia and Kentucky families. He attended Transylvania University and taught mathematics and astronomy at the Dallas High School for a year before his graduation. His medical degree was obtained at the University of Maryland, and his internship was served in Baltimore City Hospital. In 1892 he hung out his first shingle in Dallas, having, like a true pioneer, seen the future of the city and the place which he would occupy in it. A tireless worker, he early acquired a skill in ophthalmic surgery which became widely known and brought him patients from all over the southwestern United States and Mexico. He was an unusually fine-looking man, and his sympathetic personality must certainly have aided his native ability in developing one of the large practices which were realized by only a few other pioneers of his day.

His active mind was never content with past knowledge, and he made numerous study tours to London, Paris, Berlin and Vienna to obtain new ideas and methods. At the Oxford Congress he showed his interesting collection of specimens demonstrating the structure of the vitreous and the suspensory system of the lens. One of his last trips was to Barcelona, Spain, where he was much impressed by the work of Barraquer.

It was natural that in Texas he should have had a wide experience with pterygium. This resulted in his best known contribution to ophthalmic surgery: transplanting of the pterygium into the lower fornix, a procedure still practiced by most American ophthalmologists and known the world over by his name. He was an early and enthusiastic intracapsular operator, employing a modified Smith expression with the aid of a leaf-shaped instrument with which the zonular ring was stretched and delivery of the lens aided. Delivery was beneath a bridge flap of conjunctiva with conjunctival sutures. In spite of certain apparent difficulties in the method, only four years ago I saw Dr. McReynolds perform a series of eight to ten such operations in two days with no serious complication on the table and 100 per cent delivery in the capsule.

His physical and mental vigor at that time were remarkable and continued so until almost the last. His optimism and enthusiasm were contagious, and as he told his plans for the future one was almost inclined to believe that he had succeeded in Ponce de León's quest. His last year was saddened by the death of Mrs. McReynolds, his life-long partner.

In spite of the cares of his practice and those assumed as a public-spirited citizen, he found time for many contributions to the literature. These were extremely practical and chiefly concerned with surgical problems. At the time of his death he was engaged in preparation of a book about the eyes for laymen, chapters of which has begun to appear



JOHN O. McREYNOLDS, M.D.
1865-1942

serially in *Hygeia*. He was honored in many ways. His alma mater, Transylvania, awarded him its LL.D. and Sc.D. He served on its board for many years and gave financial aid in preserving and enlarging its unique medical library. He served on citizens' committees in the interest of local political reform and for this and other services was publicly honored by the Dallas Chamber of Commerce in 1930. For his medical accomplishments he was decorated by the presidents of Cuba and Venezuela. Always interested in Pan-American relations, he was active in the Pan-American Medical Association and served as its president. He was an honorary member of the Mexican Ophthalmological Society and of the Mexican Academy of Medicine and an

active member of the American special societies and of the American College of Surgeons. He served as president of his county and state medical societies and as vice president of the American Academy of Ophthalmology and Otolaryngology and of the western section of the triological society. He was chairman of the Section on Ophthalmology of the American Medical Association in 1922. He served during World War I as surgeon to the 18th Corps Area, retiring with the rank of colonel.

Among his avocations were his orange grove in the valley of the Rio Grande and the restoration of his family home in Elkton, Ky. He is survived by an only daughter, Mrs. F. W. Wozencraft, and two grandsons.

Those who were fortunate enough to know him as a friend and to enjoy his abundant hospitality will always remember these opportunities with pleasure and will miss him keenly.

SANFORD R. GIFFORD, M.D.

WILLIAM HENRY LOWRY, M.D.

1880–1942

William Herbert Lowry, M.D., C.M., M.R.C.S., F.R.C.S. (Canada), the son of William Hugh and Ann Jane Hill Lowry, was born in Acton, Ontario, Canada, on Sept. 26, 1880. He chose to follow his father's footsteps in medicine and graduated in 1901, with the degree M.D.C.M., at Trinity University, Toronto, where his father had been gold medalist, though he had come as a boy from County Cork, in Ireland. Ann Jane Hill Lowry was born in Peru, Ontario. From Acton the Lowry family moved to Guelph in order that the children might have the educational advantages of a larger city.

Dr. William Lowry early decided to practice ophthalmology, and after his university course at Toronto he took his special training in England, at London and Birmingham. On his return to Toronto in 1906, he was appointed to the staff of the Hospital for Sick Children and in 1919 he became surgeon in chief of the ophthalmic department. In 1929 he was appointed professor of ophthalmology and head of the department at the University of Toronto, succeeding Prof. James MacCallum. Owing to ill health, he resigned in 1941 and became professor emeritus of ophthalmology, Prof. Walter Wright succeeding him.

The first World War interrupted his practice, and he served with No. 4 General Hospital in England and Salonika, Greece, in charge of ophthalmology, and his valuable work received recognition in his rank as major and later as lieutenant colonel. After the war he resumed his work in Toronto and rapidly established an extensive practice. His opinion was much sought after, and in consultation he was helpful to patient and physician alike, and his quiet manner inspired confidence. It was characteristic of him that he interrupted his summer holiday to answer an urgent call, and it was at the home of his patient that he suffered the heart attack which resulted in his death on July 13, 1942.

On April 2, 1926, he married Lorna Corrine MacKendrick, who survives him with two daughters, Ann Corrine and Lorna Beverly, and two sons, William Gordon and Alan MacKendrick. Two sisters, Mrs. Frank MacArthur, of Toronto, and Mrs. Thomas Fannin, of Vancouver, and a brother, Edwin Lowry, of Winnipeg, form the rest of his immediate family. He was a devoted husband and father, and when the stress of work permitted it, an afternoon excursion into the country with his children appealed to him. He wanted to instil in them the love he had for our woods, streams and sunshine.

As a sportsman he enjoyed the games of golf and tennis, both of which he played well, and he loved the forests and lakes of the north-

land. In hunting it was the outdoor life that he liked, and he admitted to having more interest in the ballistics of firearms than in their more usual purpose. He was an excellent shot, and his hobby was the collection of a wide variety of beautiful and accurate hunting equipment, of which he was a discriminating judge. More than a hobby for him was his summer home, situated on the river near Baysville, Lake-of-Bays. The house and grounds gave evidence of his care and planning, and the first sunny week end in the early spring would find him there to see how it had come through the winter.

His professional activity was the despair of house surgeons, who missed many breakfasts to be on hand for his early round, which was made before 8 a. m., even in winter with daylight-saving time. In the operating room he was deft and sure, with a conservative but hopeful outlook which meant much to his patients, who held him in high esteem. At his office he always had time for a little joke, and his patients came to feel they were his personal friends.

His clinical notes were meager, but his memory for details amazed his staff on many occasions. He made an effort to become familiar with the habits and the home environment of those he treated, and when pressed with work he regretted that he could not give more time to each patient. He was an earnest and painstaking teacher, and he was particularly interested in undergraduate training; even after retirement he presented prizes to stimulate the interest of students in ophthalmology.

His personal habits were spartan, and his character was a model of sincerity, kindliness and integrity, and his many friends and colleagues in all branches of the profession will deeply regret the loss of one who was always helpful, unassuming and companionable and who overlooked the shortcomings of others in a most charitable way. His occasional quiet criticism was offset by his staunch support for the loyal service of all who worked with him in his special field and in the wider realm of medicine.

ALEXANDER E. MACDONALD.